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The Nomenclature of the Bronchopulmonary Segments and Their Blood Supply

(As Revised by the Seventh International Congress of Anatomists, 1960*)

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In the summer of 1949, the International Congress of Oto-Rhino-Laryngology, meeting in London,[4] adopted names for the bronchopulmonary segments which were based largely upon the terminology devised by Jackson and Huber,[6] and upon R. C. Brock's classical studies of the anatomy of the bronchial tree.[5] This premier accomplishment by an international group has been of great value to all those who have had to

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BRONCHI

Bronchus principalis dexter et sinister
Bronchi lobares et segmentales
BRONCHUS LOBARIS SUPERIOR DEXTER
Bronchus segmentalis apicalis
Bronchus segmentalis posterior
Bronchus segmentalis anterior
BRONCHUS LOBARIS MEDIUS DEXTER
Bronchus segmentalis lateralis
Bronchus segmentalis medialis
BRONCHUS LOBARIS INFERIOR DEXTER
Bronchus segmentalis apicalis [superior]*
(Bronchus segmentalis subapicalis [subsuperior])†
Bronchus segmentalis basalis medialis [cardiacus]
Bronchus segmentalis basalis anterior
Bronchus segmentalis basalis lateralis
Bronchus segmentalis basalis posterior
BRONCHUS LOBARIS SUPERIOR SINISTER
Bronchus segmentalis apicoposterior
Bronchus segmentalis anterior
Bronchus lingularis superior
Bronchus lingularis inferior
BRONCHUS LOBARIS INFERIOR SINISTER
Bronchus segmentalis apicalis [superior]
(Bronchus segmentalis subapicalis [subsuperior])
Bronchus segmentalis basalis medialis [cardiacus]
Bronchus segmentalis basalis anterior
Bronchus segmentalis basalis lateralis
Bronchus segmentalis basalis posterior
Rami bronchiales segmentorum
Bronchioli
Bronchioli respiratorii
Ductuli alveolares
Sacculi alveolares
Alveoli pulmonis

*Square brackets denote official alternatives
†Oval brackets designate anatomical variations

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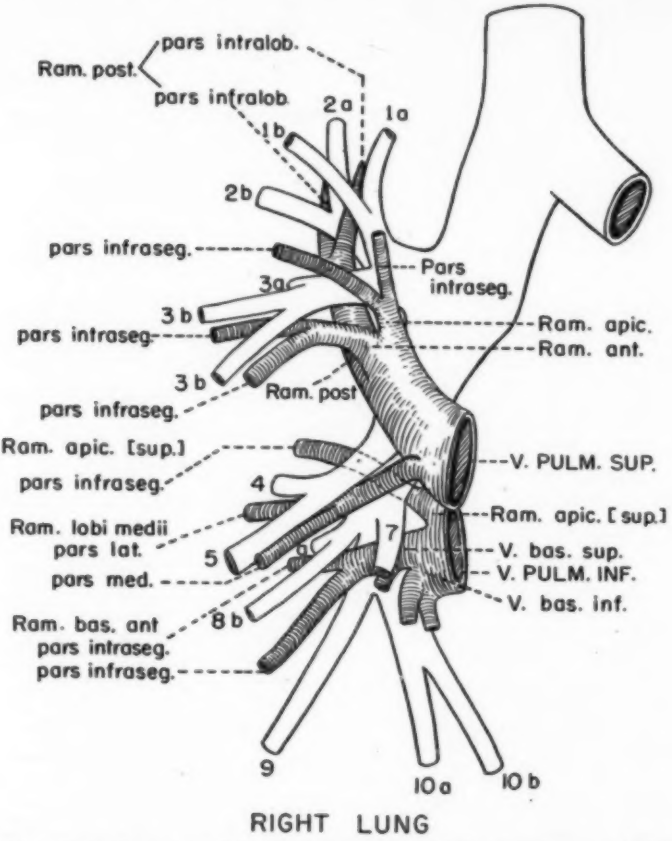
deal with the anatomy of the lungs. In 1949, however, not enough was known about the variations in bronchial pattern and in the blood supply of the segments to solve all problems of terminology. Because it was thought, for instance, that the usual mode of branching of the basal trunk of the left lower lobe was a trifurcation, the Congress omitted the left medial basal bronchus. This has caused much confusion in homologizing the segmental districts of right and left lower lobes and their blood supply. Since then it has become known that in nearly four-fifths of left lungs (110 specimens) the basal trunk divides into two stems.[2] The first of these forks usually into medial basal and anterior basal bronchi, and the second into lateral basal and posterior basal bronchi. Indeed, the left medial basal may arise alone, as the first branch of the basal bronchus, in as high as 33 per cent of lungs.[3]

Also, in 1949, it was not possible to name accurately either the segmental arteries or the principal veins that drain the segments. The first



RIGHT LUNG

FIGURE 1: Major branches of the right superior and inferior pulmonary veins superimposed upon the right bronchial tree. (Arteries omitted.) Although the veins for segments 9 and 10 have not been named by the Congress (see footnote to list of veins), they have been drawn in the figure and comparable names can be applied to them if needed.

step in this direction was taken by the Fifth International Congress of Anatomists meeting at Oxford University in 1950. There, an International Anatomical Nomenclature Committee (IANC) was appointed for the purpose of reaching agreement on the terms used in Gross Human Anatomy. It was hoped that this would end divisive nationalistic versions of anatomical terms which had sprouted up during the years between the two World Wars. This committee under the guidance of Professor George W. Corner of Baltimore (Chairman) and Professor T. B. Johnston of Guy's Hospital (Honorary Secretary) was instructed to prepare a revision of anatomical terms that should be based upon the original BNA (1895). In 1955, this revision (NOMINA ANATOMICA)[9] was accepted by the Sixth International Congress of Anatomists meeting in Paris. It contained not only the names of the segmental bronchi and bronchopulmonary segments but also the names of the principal arteries supplying these segments. Little more was done about the venous drainage than to designate intersegmental veins under such general terms as superior, medial, lateral and inferior—terms which failed to identify specific intersegmental veins, and omitted others of importance. Accordingly, the Committee of the Seventh Congress, headed by Professor Corner (Chairman) and Professor G. A. G. Mitchell of Manchester (Honorary Secretary) came to grips with this problem, among others.

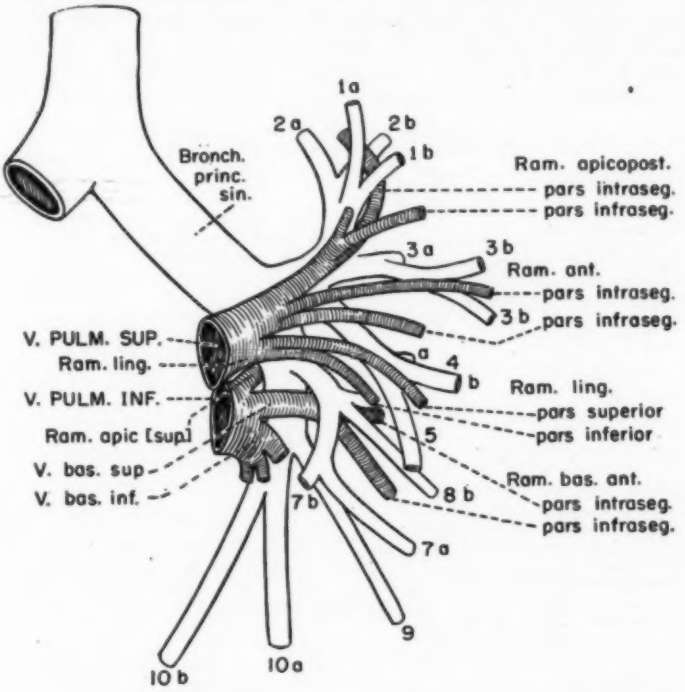


FIGURE 2: Major branches of the left superior and inferior pulmonary veins superimposed upon the left bronchial tree. (Arteries omitted.) See note in legend of Fig. 1.

Segmenta bronchopulmonalia

[PULMO DEXTER, LOBUS SUPERIOR]
- Segmentum apicale
- Segmentum posterius
- Segmentum anterius

[PULMO DEXTER, LOBUS MEDIUS]
- Segmentum laterale
- Segmentum mediale

[PULMO DEXTER, LOBUS INFERIOR]
- Segmentum apicale [superius]
- (Segmentum subapicale [subsuperius])
- Segmentum basale mediale [cardiacum]
- Segmentum basale anterius
- Segmentum basale laterale
- Segmentum basale posterius

[PULMO SINISTER, LOBUS SUPERIOR]
- Segmentum apicoposterius
- Segmentum anterius
- Segmentum lingulare superius
- Segmentum lingulare inferius

[PULMO SINISTER, LOBUS INFERIOR]
- Segmentum apicale [superius]
- (Segmentum subapicale [subsuperius])
- Segmentum basale mediale [cardiacum]
- Segmentum basale anterius
- Segmentum basale laterale
- Segmentum basale posterius

Obviously, the innumerable veins of the lungs present a perplexing situation. In the latest monograph on this subject Professor Gomez of Madrid assigns names to 79 major veins meticulously displayed in 44 figures and 26 plates.[7] A similarly detailed account of these veins with a different set of names was included in the excellent texts by

ARTERIAE TRUNCUS PULMONALIS

Sinus trunci pulmonalis

A. pulmonalis dextra
- Ramus apicalis
- Ramus posterior descendens
- Ramus anterior descendens
- Ramus anterior ascendens
- Ramus posterior ascendens
- Ramus lobi medii
  - Ramus lateralis
  - Ramus medialis
- Ramus apicalis [superior] lobi inferioris

Pars basalis
- (Ramus subapicalis [subsuperior])
- Ramus basalis medialis [cardiacus]
- Ramus basalis anterior
- Ramus basalis lateralis
- Ramus basalis posterior

A. pulmonalis sinistra
- Ramus apicalis
- Ramus anterior descendens
- Ramus posterior
- Ramus anterior ascendens
- Ramus lingularis
  - Ramus lingularis superior
  - Ramus lingularis inferior
- Ramus apicalis [superior] lobi inferioris

Pars basalis
- (Ramus subapicalis [subsuperior])
- Ramus basalis medialis
- Ramus basalis anterior
- Ramus basalis lateralis
- Ramus basalis posterior

Professor Cordier and Dr. Cabrol of Paris.[6] Instructive as these monographs are to specialists in the field it has become clear that some simpler system must be devised that relates the primary branches of the four pulmonary veins (or their major divisions) to given segments. The scheme described below (Figs. 1 and 2) was the one adopted by the Congress.

In general, it applies the segmental name to that ramus of a pulmonary vein which is closely associated at the hilum with the bronchus of that segment and which commonly receives two major tributaries from that segment—namely one from its interior (a *pars intrasegmentalis*), and one from its inferior surface (a *pars infrasegmentalis*). Usually, the latter is intersegmental; so it is permissible to substitute that

VENAE PULMONALES

(*V. pulmonalis dextra*)

- V. pulmonalis superior dextra
  - Ramus apicalis
    - Pars intrasegmentalis
    - Pars infrasegmentalis [intersegmentalis]
  - Ramus anterior
    - Pars intrasegmentalis
    - Pars infrasegmentalis [intersegmentalis]
  - Ramus posterior
    - Pars infralobaris
    - Pars intralobaris [intersegmentalis]
  - Ramus lobi medii
    - Pars lateralis
    - Pars medialis
- V. pulmonalis inferior dextra
  - Ramus apicalis [superior]
    - Pars intrasegmentalis
    - Pars infrasegmentalis [intersegmentalis]
  - V. basalis communis
    - V. basalis superior
      - Ramus basalis anterior*
        - Pars intrasegmentalis
        - Pars infrasegmentalis [intersegmentalis]
    - V. basalis inferior

(*V. pulmonalis sinistra*)

- V. pulmonalis superior sinistra
  - Ramus apicoposterior
    - Pars intrasegmentalis
    - Pars infrasegmentalis [intersegmentalis]
  - Ramus anterior
    - Pars intrasegmentalis
    - Pars infrasegmentalis [intersegmentalis]
  - Ramus lingularis
    - Pars superior
    - Pars inferior
- V. pulmonalis inferior sinistra
  - Ramus apicalis [superior]
    - Pars intrasegmentalis
    - Pars infrasegmentalis [intersegmentalis]
  - V. basalis communis
    - V. basalis superior
      - Ramus basalis anterior*
        - Pars intrasegmentalis
        - Pars infrasegmentalis [intersegmentalis]
    - V. basalis inferior

*Only the large veins related to anterior basal and medial basal segments are given since other basal segments are resected rarely.

name. A seeming exception to this pattern is presented by the posterior vein of the right upper lobe. Here the two major tributaries are (1) the large vein running beneath the surface of the posterior segment in the interlobar fissure and (2) the vein which joins it there, after emerging from the center of the lobe between anterior and posterior segments. Hence, these two tributaries have been named, respectively, the *pars infralobaris* and the *pars intralobaris* of the *ramus posterior*. These are important branches, clinically, since either of these veins may be absent congenitally and its drainage be taken over by the surviving vein. If the infralobar division drops out, the ascending arteries to the lobe are exposed (the arterial type of Appleton);[1] if the intralobar division drops out, the arteries are concealed by the enlarged infralobar division (the venous type of Appleton).[1]

In order to facilitate understanding of these patterns, diagrams of the veins and associated bronchi are presented (Figs. 1 and 2) without the complicating presence of arteries. The bronchi have been numbered according to the order adopted by the 1955 Congress. For the right upper lobe: apical (1), posterior (2), anterior (3); for the medial lobe: lateral (4), medial (5); for the right lower lobe: apical [superior] (6), medial basal [cardiac] (7), anterior basal (8), lateral basal (9), posterior basal (10). Homologous numbers have been applied to the left lung.

In conclusion, it may be stated again that the objective of the Congress in dealing with the veins of the lungs has been to settle upon simple self-explanatory terms. Although the international language of anatomy is Latin, the vernacular may be substituted for local usage.

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Pleuro-Pulmonary Manifestations of Systemic Lupus Erythematosus*

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Systemic lupus erythematosus is a generalized disorder of the fibroblastic connective tissue, in occurrence and persistence of which, autoimmunity plays an outstanding role.[1-4]

The cutaneous localization of this disease was the first to be recognized;[5] the discovery of renal,[6] cardiac,[6-7] neurological[8] and articular involvement followed.

The high frequency of digestive involvement in the cases described by Osler[8] caused some authors to deny that they were true lupus. Recently, others,[9-12] including us[13] have noticed the high incidence of this involvement in S.L.E. Some hematological aspects of this disease have also recently been described.[14-17]

Although pleuro-pulmonary affections stand among the most frequent manifestations of this disease, they were described much later than many others and there is still much disagreement as to their true nature, significance, frequency and characteristics.

This paper will discuss pleuro-pulmonary affections occurring in 48 proved cases of systemic lupus erythematosus. We reviewed 97 records of patients from the Instituto Nacional de Cardiología, the Hospital de Enfermedades de la Nutrición and the Sanatorio San Angel, who at some time had been diagnosed as having S.L.E. Of these, we finally included 48 (29 from the Instituto Nacional de Cardiología, 18 from the Hospital de Enfermedades de la Nutrición, and one from the Sanatorio San Angel) whose disease had been proved by finding L.E. cells or by various histological methods.

TABLE 1—PROCEDURES TO CONFIRM DIAGNOSIS IN 48 CASES PRESENTED

	No. of cases:
L.E. cells only:	24
L.E. cells and autopsy:	12
L.E. cells and skin biopsy:	2
L.E. cells and renal biopsy:	1
Autopsy only:	7
Skin biopsy only:	2
Total:	48

We consider that recent studies[18-24] have sufficiently demonstrated L.E. cells to be specific, in spite of reports, reviewed by Domz et al,[25] that these cells have been found in other clinical entities. Furthermore, we have not encountered any instance in this series in which we might suspect L.E. cells to represent a false positive.

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**From the Hospital de Enfermedades de la Nutrición, México, D. F.
†Director, Sanatorio San Angel, México, D. F.

FIGURE 1

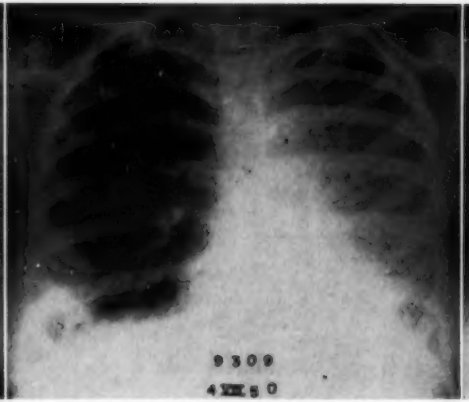

FIGURE 2

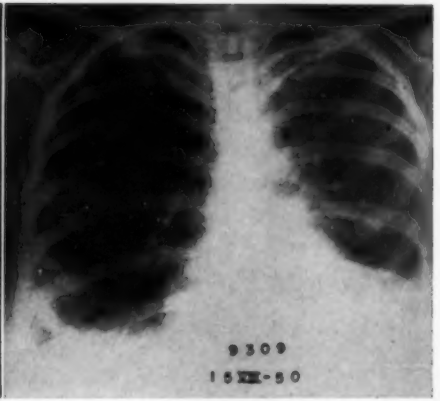

FIGURE 3

FIGURE 1: July 27, 1950. Shadows occupying the lower portion of both lungs. The haziness on the right side suggests effusion. FIGURE 2: August 4, 1950. Seven days later the left lung shows a uniform shadow of light density through which micronodular changes are noticeable. FIGURE 3: August 15, 1950. After 11 days the left shadow is almost gone. Only some haziness over the diaphragm remains. The shadow on the right side is clearer.

We believe, with Walsh and Zimmerman,[28] that some of the false positives reported have not been true L.E. cells but tart cells with a highly homogenized cromatinic pattern and, on the other hand, that some of the different entities in which L.E. cells were reported, e.g. rheumatoid arthritis, hemolytic anemia, hepatitis and liver cirrhosis, have been true lupus masquerading as these diseases.

This assumption has been confirmed later in some cases.[27-31] We also believe that hydralazine is capable of producing a peculiar reversible lupus erythematosus; the extent of this reversibility is not yet known.*

These 48 cases do not represent the total number seen in the hospitals mentioned, but only those that were informative enough at the time this study was carried out. We studied their renal, cardiovascular, pulmonary, neurological, digestive, hepatic and splenic manifestations. Cutaneous and articular involvement and also the hematoiogical and laboratory data were briefly reviewed. The complete results of this study have been reported elsewhere.[13]

Although Osler described a typical pneumonitis in three of the S.L.E. cases reported by him in 1904, not much attention was paid to pleuropulmonary involvement until Rakov and Taylor[32] published a case followed roentgenographically for years with pulmonary lesions attributable to this disease.

After these authors' communication, pulmonary and pleural involvement has been reported fairly frequently, and its high incidence has been recognized by most writers. In 105 cases reported by Harvey et al[10] the lungs were involved in 46; twenty were considered as true L.E. pneumonitis, the rest as associated phenomena. Israel[33] noticed that pulmonary lesions are too frequent to be coincidental; he found them in 20 of 22 cases. A similarly high incidence was reported by Myhre[34] who found them in 16 of 18 cases. However, we must emphasize the great variance among different writers in this regard, a variance that Bulgrin, Dubois and Jacobson[35] consider inexplicable. They found that 46.5 per cent of chest roentgenograms among 207 cases reviewed by them were negative for any abnormality.

Jessar and co-workers[11] found pulmonary lesions in 39 per cent of 216 cases collected from different sources. Much confusion arises from the fact that some of the pulmonary manifestations have not been duly recognized and have been considered by many authors as terminal, nonspecific events. Israel believed that specific pleuro-pulmonary manifestations are infrequent even when disseminated perivascular changes, chronic interstitial pneumonia and massive pleural effusions are counted as specific lesions. He stated that the commonest manifestation is an unspecific pneumonia that appears not only as a final event, but as a recurrent and migratory process.

This migratory pattern of pneumonitis noted by Israel, however, we now recognize, in the light of later reports, as characteristic of lupus; it has been described by several authors[35-38] and it has been observed by us. Tumulty[3] believes that pleuro-pulmonary manifestations of S.L.E. are often mistakenly considered as viral or bacterial pneumonia.

*Persistence of the syndrome recently has been demonstrated (*J.A.M.A.*, 173:657, 1960).

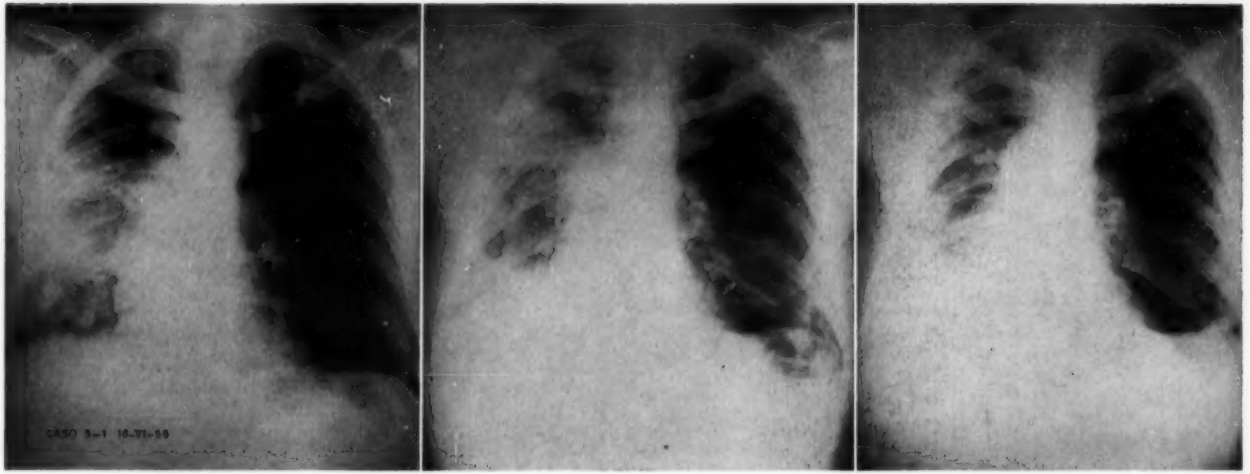

FIGURE 4 FIGURE 5 FIGURE 6

FIGURE 4: June 16, 1955. Large shadow of uneven density covering the right base, involving more than half of the right field. FIGURE 5: July 7, 1955. Twenty days later the involvement of the right lung changes, invading areas of the upper and lower lobes not involved before. On the contrary, the area occupied before becomes clearer. FIGURE 6: July 14, 1955. One week later, there is an extensive shadow covering the whole right lung. Its density is uniform although the base shows a limited area of greater density. A new shadow appears in the left costo-phrenic angle. Dextrocardia.

Of our 48 patients, 38 (70 per cent) had clinical or radiological manifestations of respiratory involvement during the course of their disease. Seven of them were included in a previous communication by Falomir[40] on roentgenographic chest changes in S.L.E.; another case with outstanding pleuro-pulmonary involvement was previously reported by one of us;[41] it is included here because of this and its long roentgenographic follow-up.

A comparison between the incidence of pleuro-pulmonary involvement and that of other organs is presented in Table 2.

TABLE 2—ORGANIC INVOLVEMENT IN 48 CASES OF S.L.E.

Site:	Number of Cases:	Per cent:
Kidney:	42	87
Joints:	40	83
Skin:	39	81
Lungs and pleura:	38	79
Heart:	34	71
Digestive tract:	28	58
Nervous system:	15	31

Besides this there was hepatomegaly in 33 per cent of our cases, splenomegaly in 21 per cent, anemia in 68 per cent and leukopenia in 40 per cent. There was fever in 87 per cent and weight loss in all the patients. These figures resemble more or less those reported in the literature.

Respiratory symptoms were frequent, cough being the most constant. It occurred in 44 per cent of our cases and was productive in two thirds of them. Expectoration was usually mucous, white and sometimes bloody. Hemoptysis occurred in five cases; this symptom may be due to acute arteritis of the pulmonary vessels or cavitation following anemic necrosis of affected tissue.[42] The respiratory symptomatology is presented in Table 3.

TABLE 3—RESPIRATORY SYMPTOMS FOUND IN 48 CASES OF S.L.E.

	Number of cases:	Per cent:
Cough:	21	44
Dyspnea:	18	37
Expectoration:	14	29
Chest pain:	12	25
Hemoptysis:	5	10

It is noteworthy that chest pain, considered by some as the commonest respiratory symptom,[36,37] was not frequent in this series.

It is important to stress, as was done by Moersch and co-workers[38] that extensive pulmonary involvement may occur without any respiratory symptoms. This is also true of the physical findings, which are usually scarce even in the presence of outstanding radiological changes.

TABLE 4—PHYSICAL FINDINGS IN 48 CASES OF S.L.E.

	Number of cases:	Per cent:
Pleural effusion syndrome:	11	30
Broncho-alveolar rales:	8	17
Pleural rub:	1	2
Bronchial rales:	1	2

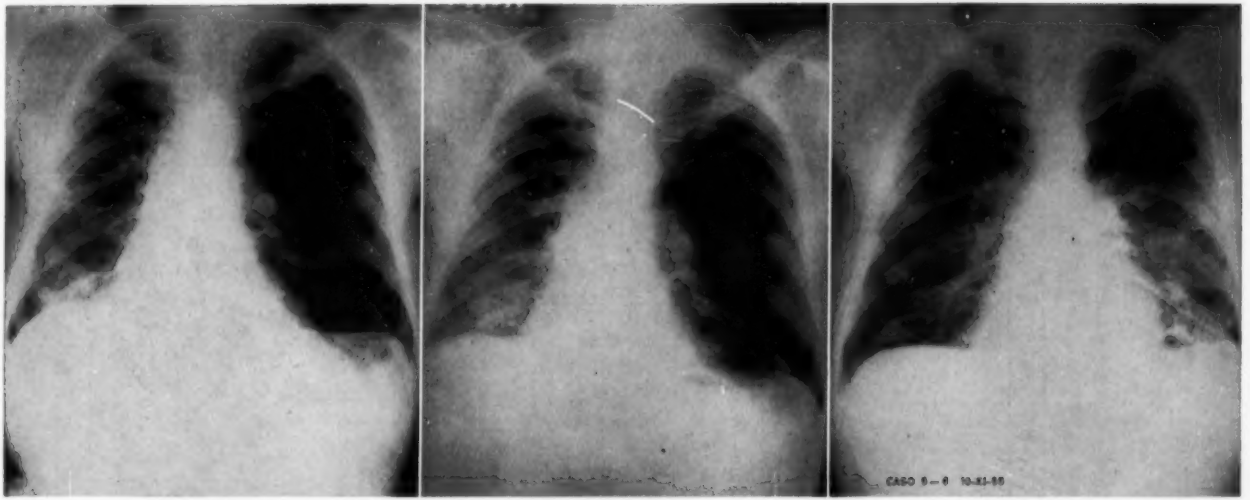

FIGURE 7 FIGURE 8 FIGURE 9

FIGURE 7: August 12, 1955. After one month, the tranparency of the right lung is almost complete. Only a small shadow remains at the right base. The heart is almost in normal position. **FIGURE 8:** September 7, 1955. Twenty-six days later, a round shadow is observed at the right base. There are old calcifications near the hilus. **FIGURE 9:** September 10, 1955. Now, the left lung is the one involved. Extensive shadow covers more than half the left field, particularly the lower lobe.

It may be seen from Table 4 that physical findings are scarce compared with the high frequency of pleuro-pulmonary involvement and that the pleural effusion found in radiology in 21 cases was large enough to be clinically detected in 11 of them.

The onset of respiratory symptoms in the course of the lupus could be determined in 24 patients; it was initial in 10 cases, and final in only three. In four, although not exactly initial, symptoms appeared in the first half of the course and in seven during the second half. This confirms Israel's[25] and others'[43,44] points of view that pulmonary manifestations do not appear, as would a bacterial complication, only in the final stage of the disease, but that they may occasionally initiate the symptomatology.

Since respiratory symptoms and the data obtained by physical examination are scarce, one might expect the same to be true of radiological changes; however, these are rather frequent and varied and silently reflect the severity of the disease. The pulmonary parenchyma shows three fundamental radiological patterns: a micronodular infiltrate that may be so fine as to resemble ground glass; pneumonic consolidation (a frequent finding), and the linear shadows of atelectasis, characteristically located in the lower lobes.

Little emphasis has been laid on the diffuse micronodular infiltrate; Purriel and co-workers[45] in a study of 15 cases do not mention this pattern, neither do Moersch et al,[26], Cordasco and associates,[46] Harvey and co-workers[10] and Turiaf.[47]

Banyai and Peabody[27] on the other hand, note the frequency of this micronodular infiltrate; Ellman and Cudkowickz[48] found a reticular pattern in one of their cases and later Ellman[49] speaks of a chronic interstitial fibrosis that he believed to be dependent on a diffuse arteritis related to the Hamman Rich syndrome; Robles Gil,[50] Bulgrin and coworkers[35] and Thorell[51] mention it, Fricsay[52] describes it in detail and Falomir,[40] after studying seven of the cases that we present here, gives them great importance.

In fact, we found the micronodular infiltrate to be one of the most frequent radiological lesions of the pulmonary parenchyma. It is a fine, ground glass mottling, often basal or more dense at the base that tends to change its location, disappears easily and is frequently associated with small pleural effusions that are also changeable. Fricsay[52] considered these infiltrates as specific of S.L.E. and believed that they must be differentiated from those attributable to pulmonary congestion, their fundamental characteristic being the ease with which they migrate and disappear.

This migratory character has also been described in the pneumonic infiltrates and we have been able to confirm it in this series.

Pneumonic infiltrates are also among the lesions produced by S.L.E.; Moersch, Purnell and Good[26] encountered them as the most frequent radiological manifestations in the pulmonary parenchyma, and noticed their changing character; Israel found them in 15 of the 22 cases that he studied and Banyai and Peabody consider them, together with the miliary infiltrate, as the most important lesions.

It is worthwhile to insist upon the astonishing migratory character of these lesions and the fact that in spite of their being roentgenologically impressive, they usually give only scarce symptoms and only a few rales are noticeable on auscultation.

This discrepancy between the roentgenological changes and the physical findings is of much importance.

Thorell[51] described small linear shadows, mainly basal, as common on S.L.E.; they were similar to those considered as atelectatic by Fleischner et al.[52] This observation has been confirmed by Ellman[49] and Myhre.[34] Tumulty[3] believes them to be the result of the organization of connective tissue in the intra-alveolar spaces. It is our belief however that these linear shadows, frequently taken as evidence of atelectasis, represent intersegmentary effusions present in lung infarction as well as in lupous manifestations of the lung. These linear shadows were found in four of our cases.

Besides changes that we consider the result of lupous involvement itself, there may often be found those secondary to congestion and left ventricular failure as a result of damage to the heart and kidneys. Bacterial pneumonic infiltrates can also complicate the disease, mainly in its final stages; these can be differentiated from a lupous pneumonitis by the already mentioned characters of migration and clinical silence. Furthermore, a complicating pulmonary tuberculosis may begin either before or after the S.L.E., as has been noticed by Purriel[45] and as happened in one of our cases.

The pulmonary radiological findings are summarized in Table 5.

TABLE 5—ROENTGENOLOGICAL PULMONARY FINDINGS IN 48 CASES OF S.L.E.

	Number of cases:	Per cent:
Micronodular infiltrate:	7	15
Pneumonic infiltrate:	7	15
Linear atelectasis (or intersegmentary effusion):	4	8
Vascular ectasis:	3	6
Emphysema:	2	4
Atelectasis (segmental):	2	4
Old tuberculous process:	1	2
Total of cases with lung roentgen findings:	17	

The pleura is affected more often than the lung; pleural effusions are usually small, though they may be more extensive. They are usually unilateral, but not always ipsilateral with the pulmonary involvement. They are occasionally massive and, of course non-specific. Dry pleuritis was less common in our series and in that of others (Table 6). Pleural adhesions have been described as a common sequel, often with raising and fixation of the diaphragm.[34] This we have found in several of our cases.

TABLE 6—ROENTGENOLOGICAL PLEURAL FINDINGS IN 48 CASES OF S.L.E.

			Number of cases:	Per cent:
Pleural effusion:			21	44
	Unilateral:	14		
	Bilateral:	7		
Dry pleuritis:			1	2

Purnell, Baggenstoss and Olsen[54] studied the pulmonary manifestations in 54 autopsies of S.L.E. and found bronchopneumonia, hemorrhage, pleural effusion, pulmonary edema, pneumonia and congestion in more than half of them. Rakov and Taylor[32] and Baggenstoss and coworkers[33] described and lent particular importance to chronic interstitial pneumonitis, often a cause of atelectasis. Baggenstoss[33] also described the existence of a basophilic mucinous edema in the alveolar walls and peribronchial and perivascular tissues. In seven patients with lupous pneumonitis, Harvey et al[10] found characteristic changes consisting of hyalin membranes in the alveoli, focal necrosis of the alveolar walls with capillary thrombosis, areas of interstitial organized pneumonia, hemorrhage and bronchiolar metaplasia. They considered that the nature of these lesions made them capable of producing focal atelectasis and, when they were severe, respiratory insufficiency.

These changes, like others found in the lungs are not specific for S.L.E.; they have been described in rheumatic pneumonitis, polyarteritis nodosa, serum sickness, and allergic pneumonitis. It may be said, with Baggenstoss,[33] that in spite of their high frequency the pleuro-pulmonary lesions in S.L.E. are not pathognomonic, but that the changes described may help to clarify the nature of the pulmonary affection.

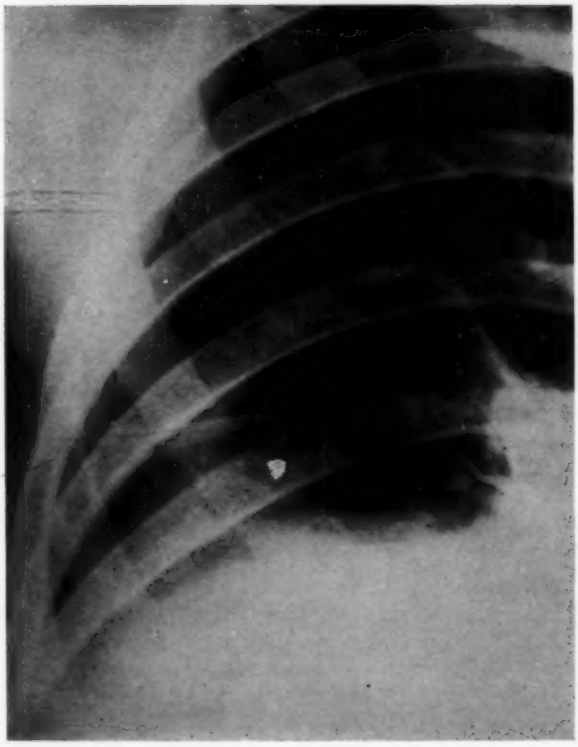

FIGURE 10: Plate-like atelectasis in the lower lobe and changes suggestive of atelectasis of middle lobe.

Nineteen cases of our series were autopsied, with the following findings (Table 7).

TABLE 7—HISTOLOGICAL PLEURO-PULMONARY FINDINGS IN 19 NECROPSY CASES OF S.L.E.

	Number of cases:
Fibrinous pleuritis:	9
Hydrothorax:	7
Atelectasis:	6
Pulmonary congestion:	6
Arteriolar lesions in parenchyma considered as lupous:	3
Acute pulmonary edema:	3
Bronchopneumonia:	2
Pneumonia :	2
Hemorrhages in lung parenchyma:	2
Cissuritis, uremic pneumonitis, necrotizing multiple thrombo-capillaritis, hyaline material surrounding arteries, thickening of the vascular advenitia and emphysema:	1 of each

The histologic and the clinical findings could not be correlated. Of the three cases that presented the respiratory picture in a final stage, necropsy was performed in two. In one of them small foci of pneumonitis with microabscess formation were found; in the other there was only passive congestion.

No satisfactory explanation for the migratory tendency of the pulmonary infiltrates has been given; although S.L.E. course may show spontaneous remissions, migration does not follow them nor is it the result of therapy. Burden and Cooper[45] believe the infiltrates to be the result of increased permeability of the vascular wall to serum and plasma. The interaction of this permeability and the compensatory mechanism could explain this puzzling migration, found elsewhere only in a few conditions like Loeffler's syndrome and Friedlaender's pneumonia, affections rather easy to discard in differential diagnosis.

SUMMARY

The pleuro-pulmonary manifestations of S.L.E. stand among the most frequent of the visceral affections of this disease.

Forty-eight cases from the Instituto Nacional de Cardiología, the Hospital de Enfermedades de la Nutrición and the Sanatorio San Angel are reviewed. In these, the diagnosis was proved by a positive L. E. cell test, which we consider specific, and/or various histologic studies, including 19 autopsies.

Symptoms, radiology and pathology of pleuro-pulmonary involvement are discussed. The lung was affected in 79 per cent of our cases; surpassed only by renal involvement.

Although respiratory symptoms and important radiologic changes were common, physical findings were usually scarce.

Three fundamental radiologic patterns were found in the pulmonary parenchyma; in seven cases a fine micronodular infiltrate; in another seven a diffuse infiltrate resembling pneumonitis, and in four, linear shadows of atelectasis. The main characteristic of these findings is the changing pattern, which is illustrated and discussed.

Hydrothorax was found by chest x-ray film in 22 cases and was important enough to be detected by physical examination in half of them.

The pathologic data at autopsy were practically non-specific, and in spite of important clinical and radiologic findings, usually little was found post-mortem. Specific lesions were found in the lungs in only three cases.

A brief correlation is attempted between the pleuro-pulmonary findings and the other clinical and laboratory data.

ACKNOWLEDGEMENTS: We are indebted to Dr. Ignacio Chávez, Director, Instituto Nacional de Cardiología and to Dr. Salvador Zubirán, Director, Hospital de Enfermedades de la Nutrición, for permission to study material from these institutions.

We are also indebted to Drs. Javier Robles Gil, José Manuel Palomir and Edmundo Rojas for their help.

We want to express our gratitude to Dr. Leo Eloesser, for kindly reviewing the English manuscript and for experienced advice.

RESUMEN

Las manifestaciones pleuro-pulmonares del Lupus Eritematoso Diseminado, son de las formas mas frecuentes de compromiso visceral en este padecimiento.

Se revisan 48 cases del Instituto Nacional de Cardiología, del Hospital de Enfermedades de la Nutrición y del Sanatorio San Angel, en los que este diagnóstico se estableció mediante el hallazgo de células L.E.; consideradas por nosotros como específicas; o por diversos exámenes histopatológicos incluyendo 19 autopsias.

Se describen la sintomatología, la radiología y la patología del compromiso pleuro-pulmonar, el que ocurrió en el 79 por ciento de los casos, sobrepasado en las formas viscerales de este padecimiento tan sólo por el riñon.

Aunque los síntomas respiratorios y las alteraciones radiológicas de importancia fueron frecuentes, los hallazgos de exploración física lo fueron poco.

Se encontraron tres imágenes radiológicas fundamentales en el paránguima pulmonar: en siete casos había un infiltrado micronodular fino; en otros siete el infiltrado era difuso, de tipo neumónico y en cuatro había atelectasia en placas. La característica primordial de estos hallazgos es la migración, lo que se ilustra y ejemplifica.

En 22 casos se encontró radiológicamente hidrotórax, y en la mitad de éstos, fué de suficiente magnitud para que se le encontrara clínicamente.

Los hallazgos histológicos fueron prácticamente inespecíficos; a pesar de su importancia clínica y radiológica, fué poco lo que se encontró post-mortem. Se encontraron lesiones específicas en sólo tres casos.

Se hace una breve correlación entre los hallazgos pleuro-pulmonares y el resto de los hallazgos clínicos y de laboratorio.

RESUMÉ

Les manifestations pleuro-pulmonaires du lupus érythémateux disséminé sont parmi les plus fréquentes des affections viscérales de cette maladie.

L'auteur passe en revue 48 cas de l'Institut National de Cardiologie, de l'Hopital des Maladies de la Nutrition et du Sanatorium San Angel. Pour ceux-ci, le diagnostic fut mis en évidence par la présence de cellules de Hargraves (que l'auteur considère comme un test spécifique) associées ou non à différentes études histologiques, comprenant 19 autopsies.

Les symptômes, la radiologie et l'anatomo-pathologie de l'atteinte pleuro-pulmonaire sont passées en revue. Le poumon fut atteint dans 79% des cas; ensuite le viscère le plus touché fut le rein.

Bien que les manifestations respiratoires et les altérations radiologiques soient banales, les signes physiques sont rares en règle générale.

Trois aspects radiologiques fondamentaux existaient au niveau du parenchyme pulmonaire: dans 7 cas, une fine atteinte micronodulaire; dans sept autres un infiltrat diffus ressemblant à une pneumonie, et dans quatre, des ombres linéaires d'atélectasie. La principale caractéristique de ces constatations est le fait qu'elles sont très variables. L'auteur en apporte des illustrations et met ces aspects en discussion.

ZUSAMMENFASSUNG

Als eine der häufigsten viszeralen Affektionen des generalisierten Lupus erythematodes erwiesen sich die pleurapulmonalen Manifestationen.

Es wird über 48 Fälle aus dem Nationalen Institut für Kardiologie, dem Hospital Enfermedades de la Nutricion und des Sanatoriums San Angel berichtet. Die Diagnose dieser Fälle wurde bestätigt durch einen positiven Lupus erytematodes-Zelltest, den wir als spezifisch ansehen und/oder verschiedene histologische Untersuchungen einschliesslich 19 Sektionen.

Diskussion über die Symptomatologie, Radiologie und Pathologie der pleuropulmonalen Beteiligung. Die Lunge war in 79% unserer Fälle betroffen; ihr folgte der Häufigkeit nach an zweiter Stelle die Niere.

Es kamen zwar Symptome vonseiten der Atmungsorgene und beträchtliche röntgenologische Veränderungen sehr oft vor, doch waren die physikalischen Befunde meist spärlich.

Die im Lungenparenchym zu findenden röntgeiologischen Erscheinungen werden in drei Gruppen aufgeteilt:

In 7 Fällen handelte es sich um kleinstknotige Infiltrate, in weiteren 7 um diffuse Infiltrate von pneumonischem Charakter und schliesslich in 4 Fällen um atelektatische Abschattungen. Das wesentliche Merkmal dieser Befunde besteht in ihrem wechselnden Erscheinungsbild. Dies wird demonstriert und diskutiert.

Ein Hydrothorax wurde mittels Thorax-Rö-Aufnahme bei 22 Kranken ermittelt und war so ausgeprägt, daß er in der Hölfte der Fälle durch die physikalische Untersuchung entdeckt werden konnte. Die bei den Sektionen gewonnenen pathologisch-anatomischen Ergebnisse waren praktisch unspezifisch, und wir fanden trotz erheblicher klinischer und röntgenologischer Befunde gewöhnlich postmortal wenig. Nur bei 3 Kranken ergaben sich spezifische Lun enherde. Es wird eine kurze Korrelation versucht zwischen den pleurapulmonalen Befunden und den übrigen klinischen und Laboratoriumswerten.

Complete reference list will appear in reprints.

High Dosage Isoniazid in Original and Retreatment Chemotherapy for Pulmonary Tuberculosis: Clinical, Electrophoretic, and Bacteriological Studies*

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Forty-five patients were observed in the study reported in this paper. Twenty-six were chronic, predominantly far-advanced subjects with previous chemotherapy (including lower dosage isoniazid); three had moderately-advanced tuberculous disease. Nineteen were chronics who had never been on a chemotherapy regimen. Of these original treatment cases, eight had far-advanced disease; nine moderately-advanced; and two minimal. The study regimen consisted of 800 mg. isoniazid and 100 mg. pyridoxine per day.

In addition to the clinical aspects of success or failure of such a regimen, the investigators were also concerned with the physiological reaction of the patients as reflected in their paper electrophoretic serum protein fractions and with the question of the virulence of the isoniazid-resistant, catalase-deficient tubercle bacilli excreted in their sputum. With respect to the latter problem, we therefore had the data with which to ascertain whether any correlation existed between the clinical, physiological, and bacteriological results obtained from monthly serum and sputum specimens from patients harboring such organisms. While the value of animal work cannot be denied, the pathogenic process in the human host is, in the final analysis, *the* criterion of virulence.

Methods

The serum protein fractionations were made with the Spinco Model R electrophoresis apparatus and methods.† Total proteins were performed with the Biuret method, according to Wolfson and Cohn.[1]

The normal values for the serum proteins employed as bases for comparison with those obtained from our patients were: total proteins—7.4 gm. per cent ±0.55, albumin—59.8 per cent ±4.2, alpha 1-globulin—4.1 per cent ±0.9, alpha 2-globulin—9.4 per cent ±1.7, beta-globulin—11.6 per cent ±1.7, gamma-globulin—15.3 per cent ±2.9, and albumin:globulin radio—1.55 (the standard deviations were calculated from the protein fraction values). These values were taken from Henry et al,[2] because they closely approximated those derived from a smaller series in our laboratory.[3] Protein data from a patient were considered abnormal if it exceeded two standard deviations from the above normal averages.

The drug susceptibility, catalase, and guinea pig tests were performed essentially as described in the Veterans Administration Tuberculosis Laboratory Methods (1955 and 1956). Two precautions were taken with respect to the animal experiments. First, pairs of guinea pigs were inoculated with suspensions from both the control and resistant culture

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tubes, so that any sensitive organisms that may have been obscured by the susceptibility testing technique might manifest themselves by a difference in the degree of disease induced in the respective guinea pigs. However, since the results from these tubes were about equal, it was assumed that we were dealing with apparently totally resistant bacillary populations. Second, the animals were sacrificed at four, six, and more than six week intervals to reveal any regressive patterns of tuberculous disease. However, one early group of guinea pigs was only autopsied well beyond six weeks, in an effort to reveal any slowly progressing disease possibly induced by resistant and catalase-deficient inocula.

Results

The roentgenographic progress of the original treatment and retreatment cases is outlined in Table 1. The distribution of the two groups

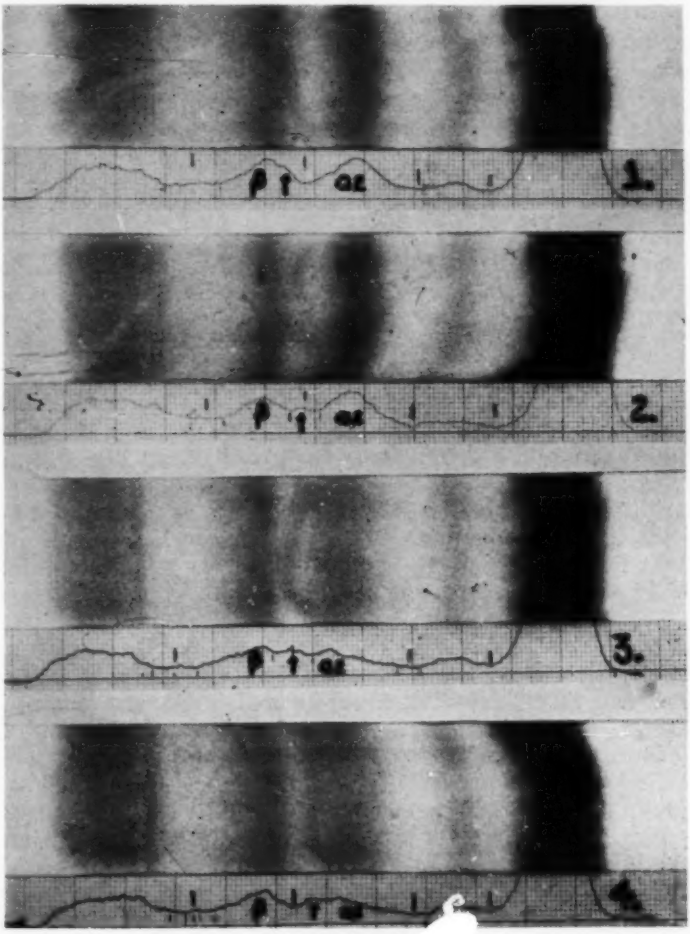

FIGURE 1

with respect to cavitary and fibrotic or exudative disease is apparent from the table. Nineteen of the 45 cases, all but two belonging to the original treatment group, showed improvement. In the original treatment group, the far-advanced fared as well as the lesser-advanced disease cases. The two improved patients in the predominantly chronic, far-advanced retreatment group did include one far-advanced case. Of the 19 original treatment cases, six were negative for acid-fast bacilli from the time they were started on high-dosage isoniazid, 10 converted to negative shortly afterwards, and three became resistant (one with sparse growth). The sputa of those that converted to negative produced a sparse initial growth in five cases and one plus or more in one fibrotic and three exudative cases. Only one original treatment patient died, and this was ascribed to cardiovascular disease; eight retreatment cases expired (one due to myocardial infarction).

Practically no toxicity was experienced with high-dosage isoniazid. The one exception was a patient who was removed from the regimen because of skin rashes. However, even in this instance, the genuineness of the complaints was suspect.

Tables 2A and 2B summarize the electrophoretic serum protein results in conjunction with some additional clinical data. The electrophoretic patterns of several, other than those judged as "improved" roentgenographically, indicated a return to normal; however, their clinical condition was diagnosed as "unchanged." Further comment will be made with respect to these below.

An analysis of the three patterns in the cavity, fibrotic, unchanged group will permit the reader to orient himself with respect to those that follow. It should be noted, to begin with, that these are "average" patterns. Table 3 illustrates the individual data from which these "averages" were derived. Morover, the individual values are "averaged" from a series of determinations on the same patient. The four cases exhibiting a normal pattern throughout the course of observation on this study are by no means to be interpreted as "cured." They are, rather, to be viewed as having achieved a condition of stability or equilibrium with respect to their disease. The deaths of two of these patients (A.B. and J.B.) will be discussed later. The organisms isolated from these were all resistant to isoniazid with no or highly diminished catalase activity. Guinea pigs inoculated with specimens from A.E.H. and A.B. exhibited a regressive pattern of disease; however, "moderate" tuberculous disease was still evident at the time of autopsy.

The second pattern indicates that the reparative processes (high beta-globulin) had gained the ascendancy before conversion to normal. One of these six cases (J.B.T.) in Table 3 represents an intermediate stage, as he had not returned to normal in the 12 months studied. However, he did also have genito-urinary tuberculosis (see below). Three of these (N.A., S.V., and J.B.T.) were isoniazid-resistant, catalase-negative; one (Y.B.) converted to resistant in the 12th month but remained catalase positive; and two (A.D.B. and A.A.C.) were sensitive (or borderline-resistant to 1 mcg./ml. isoniazid, sensitive to 5 mcg./ml.) with catalase activities varying from negative to positive depending on the particular monthly sample. Bacterial suspensions from these cases (with the ex-

ception of A.A.C., whose specimen was catalase positive) produced little or no disease in the guinea pig. However these animals were sacrificed well beyond six weeks, and remnants of tuberculous disease, particularly in the spleen, were frequently evident on gross examination.

The third pattern represents four patients in whom the tissue destructive or inflammatory (high alpha 1- and alpha 2-globulins) processes still predominate or had resumed activity, with intermittent reparative reactions (beta- and gamma-globulins) but no return as yet to a normal pattern. The cases of E.J.H. and W.S. (who died) and B.W.B. (frequent hemoptysis) will be commented on below. Two of these were isoniazid-resistant with negative or highly diminished catalase; the third was isoniazid-sensitive; and the fourth was borderline resistant with low catalase activity.

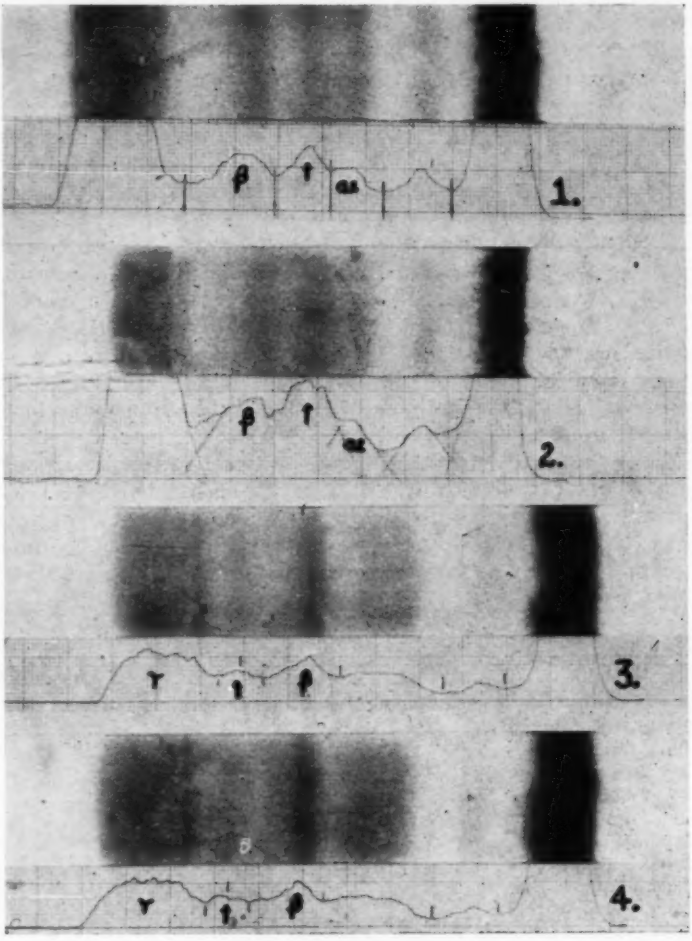

FIGURE 2

The three non-cavitary, fibrotic, unchanged cases that were resistant were also catalase positive. Two sets of guinea pigs inoculated with specimens from one of these patients proved to be tuberculous.

Thirteen of the 14 fibrotic cases showing improvement were either negative for acid-fast bacilli throughout the course of their period of observation on this study (6) or converted to negative from an initially sparse growth (7). The 14th remained positive with sparse growth. Again, it should be noted that 12 of the 14 were original treatment patients. Also of interest here is the fact that 12 (including one retreatment) of these 14 had non-cavitary disease; however, this was also characteristic of the original treatment cases. As may be seen from Table 1, 13 of the 14 fibrotic, original, treatments were non-cavitary. (The five with exudative disease had cavities.) The disease of the two improved retreatment cases was active for a relatively short time prior to administration of this drug regimen as compared to other retreatment patients (one month and 10 months). This recently active disease characterized the entire original treatment group (average of 2.7 months, ranging from 1 to 6 months and predominantly 1 and 2 months).

Four of the cavitary fibrotic cases died. However one of them (A.B.) was attributed to cardiovascular disease. The three deaths due to tuberculosis (E.J.H., W.S., and J.B.) occurred one to one and one-half years after we ceased our observations. They harbored resistant organisms with no or diminished catalase activity, and inocula from two specimens (E.J.H. and W.S.) exhibited attenuated or regressive patterns of disease in the guinea pig. (The animal results relating to J.B. were invalid.) It should also be noted that while the electrophoretic patterns of E.J.H. and W.S. indicated that tissue destructive processes still prevailed or had resumed activity, that of J.B. was normal.

The cavitary, exudative cases were generally characterized by low albumin, high globulins (all), and low A/G ratio. Those who improved converted to a normal pattern.

All five of the cavitary, exudative cases who showed improvement were again original treatments, whose disease had been active for a relatively short time before coming onto the high-isoniazid regimen. Three of these converted to negative shortly after beginning the course of therapy, and two became resistant to isoniazid. One of the latter two cases intermit-

TABLE 1—ROENTGENOGRAPHIC PROGRESS OF ORIGINAL AND RETREATMENT CASES

	Orig. Treatment			Retreatment	
Clinical Appraisal	Min.	Mod. Adv.	Far Adv.	Mod. Adv.	Far Adv.
Cav., Fibr.: Unchanged				1	13
Cav., Fibr.: Improved		1			1
Non-Cav., Fibr.: Unchanged	1	1		1	1
Non-Cav., Fibr.: Improved	1	4	5	1	
Non-Cav., Fibr.-Exud.: Impr.			1		
Cav., Exud.: Worse					5
Cav., Exud.: Unchanged					1
Cav., Exud.: Improved		2	3		
Cav., Exud.-Fibr.: Worse					1
Cav., Exud.-Fibr.: Unchanged					1
Cav., Exud.-Fibr.: Improved		1			

intermittently high; *o.t.=original treatment.

TABLE 2A—CLINICAL AND SERUM PROTEIN SUMMARY

	Clinical Appraisal	Av. Age[1]	Stage of Disease[2]	Disease Active[3]	Av. Mos. Studied	No. Cases	Serum Protein Patterns: Tot.	Alb.	α^1	α^2	β	γ	A/G	→ Norm.
Cavity, Fibrotic	Unchanged	56 (35-70)	Far-Adv. [1]Mod-Adv.	5,0	12	4	•[5]	•	•	•	•	•	•	
						6	•	L[6]	int H[7]	int H	H	•	L	7th
						4	•	L	H	H	int H	int H	L	
	Improved	42 (38-46)	F.A. & M.A.	0.2	6	2 (1 o.t.)[8]	•	•	•	•	•	•	•	
No Cavity, Fibrotic	Unchanged	43 (22-77)	Min to F.A.	0,7	5	2 (1 o.t.)	•	L	•	•	•	H	L	
						2 (1 o.t.)	•	•	•	•	•	•	•	
	Improved	52 (41-66)	M.A. & F.A.	0,3	7	6 (5 o.t.)	•	•	•	•	•	•	•	
						5 o.t.	•	L	•	int H	int H	int H	L	3rd
No. Cav., Fibr-Exud.	Improved	65	F.A.	0,2	9	1 o.t.	•	•	•	•	•	H	•	2nd

TABLE 2B—CLINICAL AND PROTEIN SUMMARY

Cavity, Exudative	Worse	54 (41-65)	Far Adv.	6,0	9	5	•[5]	L[6]	H	H	int H[7]	H	L	
	Unchanged	40	Far Adv.	7,0	8	1	•	L	H	int H	H	H	L	
	Improved	56 (35-64)	Mod Adv. & Far Adv.	0,3	8	2 o.t.[8]	•	•	•	•	•	•	•	
						2 o.t.	•	L	int H	H	int H	H	L	4th
Cavity, Exud-Fibr.	Worse	60	Far Adv.	0,6	3	1	•	L	H	H	H	H	L	
	Unchanged	24	Far Adv.	5,0	1	1	•	L	H	H	•	•	L	
	Improved	38	Mod. Adv.	0,1	8	1 o.t.	•	L	•	•	•	•	L	2nd

[1]At start of regimen; [2]all chronics; [3]years, months at start of regimen; [4]month converted to normal pattern; [5]• (dot)=normal; [6]L=low; [7]int. H=intermittently high; [8]o.t.=original treatment.

tently produced organisms of high and low catalase activity after becoming resistant. A pair of guinea pigs inoculated with a resistant, catalase-positive strain produced disease which regressed somewhat; however, more than "moderate" disease was still evident at autopsy. (The death of this patient was ascribed to heart disease.) The catalase activity of suspensions from the second case diminished after becoming resistant, however they produced progressive disease in the guinea pig.

Four of these cavitary, exudative patients who deteriorated were resistant with little or no catalase activity; two were borderline resistant and catalase positive. The two in the "unchanged" category were borderline resistant and exhibited reduced catalase production.

Six patients with cavitary, exudative disease died. However, one of them who had been judged "improved," succumbed to myocardial infarction three months after his period of observation on this study. This was the only death in the original treatment group. Another died one year after being transferred onto another regimen. Three were isoniazid-resistant with no or diminished catalase activity, whose bacterial suspensions induced tuberculous disease which regressed in guinea pigs. However this regression varied in degree, and "moderate" disease was still evident in two cases at the time of sacrifice of the animals. Moreover, several specimens from another cavitary, exudative case who did not expire during the course of our study produced the entire spectrum of disease patterns from no disease to progressive disease (even death) in the guinea pig. The reader's attention is called to the fact that the serum protein pattern of one of these exhibited only a high gamma-globulin (at least during the short period of observation), which we would ordinarily interpret as the reflection of a good fibrotic process or immunological response.

Despite the above general observations concerning attenuated or regressive patterns of tuberculous disease in the guinea pig, it should be noted that not only was some "moderate" and even progressive disease produced in the experimental animal, but, more important, deterioration and death of patients harboring catalase-deficient organisms occurred. The so-called "moderate" disease is only an arbitrary designation on a virulence scale employed by the authors for comparative purposes only in this study. We have observed such "moderate" disease produced in the guinea pig by isoniazid-sensitive, catalase-positive organisms. Furthermore, we question whether one may generalize about the virulence of bacilli harbored by some resistant cases, in which not only was variation in catalase activity noted for colonies from a single culture and from tube to tube on a definite date, but also from one monthly specimen to another. It would seem, at least in such cases, that any judgment would be referable to the particular organisms isolated on a definite date. This further complicates the problem of the virulence of such organisms.

In the original treatment group, where the only opportunity for observing the comparative progress of moderately- and far-advanced patients existed, no differences were observed clinically or electrophoretically.

We also attempted to ascertain whether coexisting diseases or complications influenced the course of the tuberculous disease, as reflected in

the electrophoretic serum protein patterns. Three of the patients (including A.E.H.) were diabetic; however, their protein pictures showed no significant deviations from those of other tuberculous cases in the same clinical categories. The two cardiac patients (including A.B.) have been mentioned above in the discussion of the deaths occurring on this regimen; their patterns had been normal for some time prior to expiration. Again, no apparent unusual effects were induced by silicosis in two cases, nor did the emphysema, gastro-intestinal ulcer, or arthritis (A.A.C.) of three others produce any observable influences. Whether the genito-urinary tuberculosis of J.B.T. was responsible for the failure of his pattern to return to normal (as did the others in his clinical classification—see Table 3) is a moot question, but it could very well represent a type of pattern intermediate between the second and third general types of the cavitary, fibrotic, "unchanged" group. The gamma-globulin in the pattern of a pleural effusion case was significantly high before its return to normal limits. While none of the non-cavitary, fibrotic, "improved" cases had such a consistently high gamma fraction, it was characteristic for two of the "unchanged" patients in the non-cavitary, fibrotic category. B.W.B.'s frequent hemoptyses seem to have been reflected in his protein patterns by a consistent predominance of tissue destruction (high alpha 1- and alpha 2-globulins) and a failure of the reparative processes to manifest themselves. A.D.B.'s resective surgery (sixth month) was followed by a significant rise in globulins (except gamma) and fall in albumin, which returned to normal by the 10th month of observation on this regimen.

Figures 1 and 2 illustrate some anomalous serum protein fractions encountered in the course of our electrophoretic work. What appear to

TABLE 3—DATA ON PATIENTS WITH FAR-ADVANCED, CAVITARY, FIBROTIC PULMONARY TUBERCULOSIS, CLINICALLY JUDGED AS "UNCHANGED"

Patient	Age	Disease Active[1]	Mos. Studied	Serum Protein Pattern							
				Tot.	Alb.	α^1	α^2	β	γ	A/G	Normal[2]
C.E.F.	39	3,9	13	•[3]	•	•	•	•	•	•	
A.E.H.	51	6,0	12	•	•	•	•	•	•	•	
A.B.	55	7,7	9	•	•	•	•	•	•	•	
J.B.	59	8,5	1	•	•	•	•	•	•	•	
N.A.	68	5,0	15	•	L[4]	•	H	H	•	L	7th
S.V.	61	6,6	16	•	L	int[5] H	int H	H	•	L	8th
Y.B.	68	1,9	14	•	L	•	H	H	•	L	3rd
A.D.B.	35	1,0	16	•	L	H	int H	H	•	L	10th
A.A.C.	50	4,1	18	•	L	int H	int H	H	•	L	7th
J.B.T.	70	2,9	12	•	L	int H	int H	H	•	L	
E.J.H.	43	6,5	12	•	L	int H	H	•	int H	L	
W.S.	65	2,1	3	•	L	H	H	•	•	L	
J.L.F.	58	5,0	8	•	L	H	H	H	H	L	
B.W.B.	63	5,0	10	•	L	H	H	•	•	L	

[1]Years, months at start of regimen; [2]month converted to normal pattern; [3]• (dot)= normal; [4]L=Low; [5]int. H=intermittently high.

be three different fractions, in addition to albumin and alpha 1-, alpha 2-, beta-, and gamma-globulins, are presented. In Figure 1, a lightly-staining, curved (or crescent-shaped) one is discernible between the alpha 2- and beta-globulins. This occurred in 24 of the 45 cases in our study, rarely in some and frequently in others. It was also found in one presumably normal person in the course of establishing a set of normal electrophoretic serum proteins in this laboratory.[3] Although this fraction is distinct on the first strip, it is not very apparent on the graph. This is due to the fact that the central portion of its curve is in close proximity to the beta-globulin area of density. While the height of the paper strip is 30 mm. that of the densitometer scanning slit is only 19 mm.; the portions of the fraction beyond the central area are thereby not scanned and recorded although they may be clear of the beta-globulin fraction. Strips two and three exhibit this intermediate fraction clearly in a central position, and they are thus reflected in the graph. The closeness of the fraction to the alpha 2-globulin in strip four is revealed as an additional hump on the trailing edge of alpha 2. The position of the intermediate fraction, or whether it will be revealed at all, often seems to depend on the distance that the serum specimen has migrated. In Figure 2 a darkly-staining, non-curved fraction appears on strips one and two between alpha 2- and beta-globulins. This appeared only intermittently in one patient and also seems to be distinguishable from the previously discussed fraction by the greater concentration in which it appears. A distinction on this basis, however, is admittedly superficial and not necessarily valid. The third and fourth strips reveal a fraction between beta- and gamma-globulins that consistently occurred in the electrophorograms of one patient. These fractions have as yet not been further investigated.

SUMMARY

Forty-five patients with pulmonary tuberculosis, undergoing both original and retreatment chemotherapy, received 800 mg. isoniazid and 100 mg. pyridoxine daily. The original treatment cases did well on this high dosage regimen; however, it proved to be of little value for those who had not responded to previous chemotherapy.

The physiological reaction to the disease process could generally be followed by the serum protein electrophoretic patterns. The exudative process was reflected in elevated alpha-globulins and the reparative or fibrotic processes, in high beta- or gamma-fractions. Low albumins accompanied such variations from the normal electrophorogram. The total protein values never varied from the normal range, at most approaching the upper limits of this range.

The observation of progressive disease in patients harboring catalase-negative, isoniazid-resistant tubercle bacilli contravenes any generalization concerning the attenuation or avirulence of such organisms.

RESUMEN

Se trataron 45 enfermos de tuberculosis pulmonar originalmente o con tratamiento de repetición, proporcionándoles 800 mg. de isoniacida con 100 mg. de piridoxina diariamente. A los enfermos con tratamiento original, el tratamiento si fué provechoso, pero no fué sino de poco valor para los que no habían respondido bien al tratamiento previo.

La reacción fisiológica a la enfermedad pudo en general, seguirse según los aspectos electroforéticos de la proteína en el suero. El proceso exudativo se manifestó por una elevación de las globulinas alfa y el proceso de reparación o fibroso por elevadas fracciones de beta o gama. Las albúminas bajas acompañaban a tales variaciones del electroforograma normal. Los valores totales de la proteína difirieron de lo normal y cuando mas se aproximaron a los límites superiores del tenor de las proteínas.

La observación de enfermedad progresiva en los enfermos que alojan en su organismo bacilos catalaso-negativos e isoniacido-resistentes se contrapone a cualquier generalización respecto de la atenuación o la virulencia de tales gérmenes.

RESUMÉ

45 malades atteints de tuberculose pulmonaire, subissant un traitement chimiothérapique aussi bien pour la première fois qu'après reprise du traitement, reçurent 800 mg. d'isoniazide et 100 mg. de pyridoxine chaque jour. Les malades soumis à ce traitement pour la première fois répondirent bien à ce régime de haut dosage; cependant, il se montra de peu d'effet pour ceux qui n'avaient pas répondu à une chimiothérapie antérieure.

La réaction physiologique au processus de la maladie pouvait généralement être suivi par les tracés électrophorétiques des protéines du sérum. Le processus exsudatif était reflété par l'élévation des alpha-globulines, et les processus réparateurs ou fibreux par élévation des fractions bêta-ou gamma-. Des taux d'albumines faibles accompagnaient de telles variations de l'électrophorèse normale. La valeur des protéines totales ne varia jamais par rapport au taux normal, approchant au maximum les limites supérieures de ce taux.

L'observation d'affection évolutive chez des malades dont les bacilles tuberculeux étaient résistants à l'isoniazide, et à catalase négative, interdit toute généralisation au sujet de l'atténuation ou la modification de virulence de tels germes.

ZUSAMMENFASSUNG

45 Kranke mit Lungentuberkulose, bei denen die Chemotherapie als Erst- wie als Wiederholungs-Behandlung erfolgte, erhielten täglich 800 mg INH und 100 mg Pyridoxin. Die in Erstbehandlung stehenden Fälle gediehen gut bei dieser hohen Dosierungsart; eine solche Methode erwies sich jedoch als von geringem Wert bei denjenigen Kranken, die auf vorherige Chemotherapie nicht angesprochen hatten.

Die physiologische Reaktion auf den Krankheitsprozess ließ sich allgemein verfolgen an Hand der elektrophoretischen Serum-Protein-Wertreihe. Der exsudative Prozess kam zum Ausdruck in Form erhöhter Alpha-Globuline und die reparativen oder fibrotischen Prozesse in hohen Beta- oder Gamma-Fraktionen. Niedrige Albuminwerte begleiteten solche Varianten des normalen Elektrophorogrammes. Die Gesamteiweißwerte wichen niemals vom Normalen ab und erreichten meistens die obere Grenze.

Die Beobachtung von fortschreitender Erkrankung bei Patienten mit Katalasenegativen, auf INH resistenten Tuberkelbazillen erschüttert jede Verallgemeinerung, die dis Abschwächung oder Avirulenz solcher Organismen betrifft.

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POSSIBILITIES FOR PREVENTION OF CARDIAC FAILURE IN PULMONARY EMPHYSEMA

Addendum to Current Therapy

In reviewing the evidence which supported the value of restoration of diaphragmatic function in patients with pulmonary emphysema, I neglected to include the contributions of Dr. Ricardo Rimini who reported as early as 1945 that the pulmonary ventilation was significantly lowered when this type of case was placed in the head-down position.[1,2,3]

The importance of substitution of diaphragmatic instead of costal respiration was made additionally clear by studies from our clinic, in which it was shown that diffusion of oxygen and CO_2 was not impaired even though the minute volume of breathing was consistently diminished, when patients with diffuse obstructive pulmonary emphysema were tilted head-down at an angle of 16 to 18 degrees.

The additional bibliography pertaining to regulation of pulmonary ventilation in this clinical entity appears in the "Summary of Current Therapy," *Dis. Chest,* 37:687, 1960.

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Evaluation of Lung Volumes and Intrapulmonary Gas Mixing in Diseased and Normal Children*

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The evaluation of pulmonary function is particularly helpful in the clinical management of long-term respiratory diseases of childhood such as cystic fibrosis of the pancreas with pulmonary complications, asthma, and respiratory poliomyelitis. Clinical studies coupled with physiological measurements of pulmonary function help to determine: (1) the evolution of pulmonary disease processes; (2) the progress of therapy programs; and (3) the programming of energy demands. Furthermore, important serial changes can be appreciated in lung compartition and functional evaluation.

A renewed interest in the physiology of the child's pulmonary function has developed in the last decade. This has been stimulated by the clinician's desire to use physiological measurements in evaluating disease states. Several studies of total lung volume and its subdivisions in healthy children have been published in an effort to establish useful comparative values for ill children (Table 1). It appears that significant variations are imposed by choice of techniques, by body positioning, and by other factors. Comparisons in health and disease are therefore best made by use of identical methods among individuals as much alike in body size and age as possible.

Attempts also have been made to extend functional evaluation to include intrapulmonary gas mixing and thereby develop standards for judging impairment in lung gas distribution. Several methods of quantitating intrapulmonary gas mixing have appeared in the literature.[1-4] Several variations greatly influence distribution indices that are dependent upon time and volume of ventilation, and that must be determined during very steady or basal states. The clearance equivalent as used by Becklake,[5] Lundin,[6] and Luft[7] appears to offer one means of correcting for these variations in lung volume and for naturally large differences in depth and rate of quiet breathing found among healthy subjects in a steady state.

The determination of the total lung capacity and its subdivisions and the efficiency of intrapulmonary gas mixing in 50 healthy children and 21 children with various types of chronic pulmonary diseases are reported and contrasted.

Method

Subjects: The 50 normal children in this study ranged in age from 6 to 13 years. Their physical characteristics are shown in Table 3. The children in the pathological series were obtained from the outpatient

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clinic of the Texas Children's Hospital and from the Southwestern Poliomyelitis Respiratory and Rehabilitation Center. Table 4 presents the physical characteristics and pathological classification of these children.

Methods of Determinations: The lung compartments obtained from the vital capacity maneuvers were determined with a 9-liter Collins spirometer. All subjects were examined in the supine position and multiple determinations of all values were made.

The functional residual capacity was determined by the open circuit nitrogen washout technique using 100 per cent oxygen according to Luft's[7] modification of the technique described by Darling.[1] The circuit used in this study is depicted in Figure 1. The FRC was calculated by the formula: $FRC=[(V_E+3.60)\ F_{EN_2}/F_{AN_2}]-0.22$. In this formula V_E represents the total volume of expired gas collected in the 120-liter Tissot spirometer at the end of the washout procedure; F_{EN_2} the fractional concentration of dry phase nitrogen in the 120-liter spirometer at the end of washout; and F_{AN_2} the fractional concentration of alveolar nitrogen prior to the washout (79 to 80 per cent). The amount of nitrogen cleared from the blood and tissues during the short test period (usually less than 3 minutes) was not calculated. On the basis of well documented studies it was probably negligible for the brief duration of this test.[6] The value, 3.60 liters, represents the volume of dead space between the valve (Fig. 2) and the bell of the 120-liter spirometer, which contained 100 per cent oxygen before the washout. The value, 0.22 liters, represents the instrumental dead space between the subject's airway, the oxygen reservoir at the inspiratory valve and the collecting reservoir at the expiratory valve.

Clearance equivalent was calculated from the following formula:

$$CE=CV(1-D'/TV)/FRC.$$

In this formula, CV (clearance ventilation) is the volume, in liters of 100 per cent oxygen, required to dilute the nitrogen in the FRC to the one per cent level as measured from breath by breath analysis; FRC is the function residual capacity; D' is instrumental dead space; and TV is average tidal volume during the washout. The factor (1−D'/TV) repre-

TABLE 1—MEAN LUNG VOLUMES IN NORMAL CHILDREN REPORTED BY DIFFERENT AUTHORS

Year - Author	Position	No. Sub.	Age (Yrs.)	V.C. (L.)	F.R.C. (L.)	T.L.C. (L.)	F.R.C./T.L.C. Mean	F.R.C./T.L.C. S.D.	Method	Ref. No.
1938—Robinson*	Supine	29	6-14	—	—	—	.389	—	O_2 dilution	11
1952—Morse, et al	Supine	94	11-17	3.76	1.50	4.19	.361	±.05	O_2 dilution	13
1956—Engstrom et al.	Seated	93	6-14	2.60	1.44	3.32	.429	±.037	H_E dilution	11
1957—Marshall**	Seated	5	9-12	2.02	1.19	3.00	.412	±.13	H_E dilution	18
1958—Helliesen† et al.	Seated	85	5-17	2.58	1.88	3.60	.522	±.05	H_E dilution	12
1959—Andrewes††	Seated	27	6-13	—	1.25	—	.443	±.047	H_E dilution	4
1959—Study	Supine	50	6-13	2.19	1.25	3.01	.417	±.05	N_2 Washout	—

*As reported by Engstrom, et al.[11]

**Calculated from the author's data.[18]

†As predicted for a 145 cm. child by the author's formula.[12]

††Estimated from the author's graph.[4]

TABLE 2—ANALYSIS OF THE VARIATION OF THE METHOD

Determination	N	p	Standard Error of the Measurement	Per Cent of the Mean
FRC	124	45	±0.090 L.	7.2%
CE	124	45	±1.3	11 %

sents a correction for the effect of instrumental dead space on clearance ventilation. This correction may be of significant magnitude when the instrumental dead space/tidal volume ratio is large.[9]

Variation of the Method: The difference to be expected between successive determinations on one person (standard error of measurement) was determined using the formula:

$$S=\sqrt{\frac{\Sigma(X_1-\overline{X}_1)^2+\Sigma(X_2-\overline{X}_2)^2\ldots+\Sigma(X_p-\overline{X}_p)^2}{N-p-1}}$$

In this formula, and in Table 2, N is the number of determinations; p is the number of subjects; X is the value of a single determination, and $\overline{X}$ is the mean of the determinations on a single subject.

Results

Table 2 indicates that for a subject with an FRC of 1.25 liters, a technical error of ±7.2 per cent is possible. This analysis was done on the FRC as an estimate of instrumental and technical error with the assumption that a normal child's FRC remains reasonably constant on successive determinations. The standard error of FRC determination is of the same magnitude as that found by other authors using the open circuit

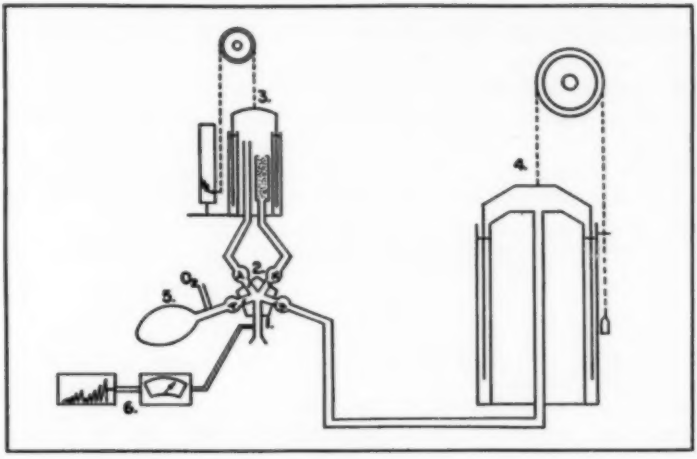

FIGURE 1: Schematic diagram of open circuit nitrogen washout and spirometric apparatus. 1. Mouthpiece-connecting tube (80 ml.), 2. Valving system (140 ml.), 3. 9-liter Collins spirometer, 4. 120-liter Tissot spirometer, 5. Oxygen source and bag reservoir, 6. Nitrogen meter and recording instrument. During the steady state the patient breathes through the small spirometer circuit. At the end of a normal expiration the valves are turned to connect the patient to the oxygen bag and the Tissot spirometer. All the nitrogen in the patient's FRC and in the instrumental dead space (0.22 L.) is collected in the large spirometer. The connection between the valves and the Tissot (3.6 L.) was previously flushed with oxygen. A small sample of expired air was diverted to the nitrogen meter by a suction pump to give a breath by breath graphical recording of the expired nitrogen concentration.

nitrogen method as well as closed circuit helium techniques in children.[4,11-13]

The results of lung volume measurements, FRC/TLC ratio and intrapulmonary gas mixing values are shown in Table 3. It was noted that the value obtained for the FRC/TLC ratio was the most reproducible and showed the least deviation from the mean. The ratio of 0.417±0.05 found in this study agrees closely with the values found by others (Table 1). The frequency (F) and tidal volume (TV) in Table 3 represent those obtained from the small spirometer circuit.

Graphical correlation of lung volumes with each of the physical characteristics was done. This analysis paralleled other authors' findings in that the various lung volumes correlate best with height.[12,13]

The median values for lung volumes in the 21 diseased children studied are reported in Table 4. Figure 2 represents the relation of the pathological clearance equivalent to the mean and standard deviations of this value for normal subjects.

Discussion

Clinical evaluation of pulmonary function in children has classically depended upon the measurement of lung volumes, particularly the vital capacity, but the reliability of these determinations in young children has been questioned because cooperation may be difficult to obtain in these subjects. However, in this study it was found that children were extremely co-operative. With this cooperation, reproducible maximal vital capacity results were obtained. In spite of this reliability it was concluded, due to the wide range of normal variability of the vital capacity, that lung volumes alone did not allow adequate evaluation of pulmonary function.

In addition to volume measurements, the ratios FRC/TLC and RV/TLC have been found to be of value in assessing pulmonary status. With this group of children, however, difficulty in obtaining a reproducible ERV was shown by a coefficient of variability (Co. V.) of 47 per cent. The FRC, however, had a coefficient of variability of only 28 per cent which is the same as that of the TLC. For this reason, it was decided that the FRC/TLC was of more value for comparative purposes. Other workers have reported this same variability in RV determinations.[7,11]

In addition to lung volumes and intervolume relationships, it is highly desirable to employ a functional criterion to estimate pulmonary status and to guide treatment of chronic pulmonary disorders. As far as present experience permits, clearance equivalent may be said to serve as a functional index reflecting intrapulmonary gas mixing. It has the advantage over the widely used intrapulmonary mixing index of excluding the 7-minute time factor. In all but one of the pathological subjects the expired nitrogen concentrations reached 1 per cent within four minutes. Obviously 7-minute samples would not distinguish between the degree of involvement in these children as

TABLE 3—RESULTS IN 50 NORMAL CHILDREN

Physical Characteristics

	Sex	Age Yrs.	Age Mos.	Height (Ins.)	Weight (Lbs.)	B. S. A. (Sq. M.)	A. P. Dia. (Ins.)	Circ. (Ins.)
Range	32 M 18 F	6 to 13	2 to 10	40.0 to 68.0	46 to 145	.84 to 1.72	4.5 to 7.2	22.5 to 33.0
Median	—	9	0	54.5	74	1.11	5.8	26.0
Mean	—	9	3	53.9	78.7	1.16	5.5	27.2

Lung Volumes and Intrapulmonary Gas Mixing Values

	I.C. (Liters)	E.R.V. (Liters)	V.C. (Liters)	F.R.C. (Liters)	T.L.C. (Liters)	F.R.C. T.L.C.	F.	T.V. (Liters)	Clr. Vent. (Liters)	Clr. Eqv.
Range	1.03 to 3.18	.18 to 1.04	1.29 to 3.97	.74 to 2.31	1.92 to 5.30	.300 to .530	12 to 40	.19 to .84	6.7 to 22.8	7.2 to 14.6
Median	1.62	.38	2.05	1.18	2.83	.417	18	.45	13.6	11.3
Mean	1.72	.43	2.19	1.25	3.01	.417	19.7	.453	13.7	11.1
S. D.	±.49	±.20	±.62	±.34	±.79	±.053	—	—	±3.7	±1.9
Co. V.	28%	47%	28%	27%	26%	13%	—	—	27%	17%

does the clearance equivalent. By dividing clearance volume by FRC the resultant clearance equivalent provides a measure of ventilatory efficiency which corrects for significant differences in FRC due to age, position, and size.

The graphic record of breath by breath expired nitrogen concentration yields valuable information also. Figure 3 demonstrates sample washout patterns from each subject group. To the experienced observer, this pattern alone gives a good approximation of the subject's mixing efficiency.

The clearance equivalent does not take into account the influence of the subject's dead space. Luft has stated that, in certain instances where there was a large DS/TV ratio, it may be desirable to differentiate between dead space effect and true intrapulmonary mixing impairment by means of the alveolar clearance equivalent.[7] This value was determined and found to be more variable than the clearance equivalent.

Comparison of Normal and Diseased Children: In Table 4, it is seen that there are significant differences between the physical characteristics of the various groups of children studied. The median ages of the four groups of children range over less than three years, but there is a wide difference between weight values for the normals and the post-polio and cystic fibrosis groups. However, the lack of any significant differences in the heights of the diseased and normal children makes the differences in their lung volumes even more striking.

Comparison of normal lung volumes to those of the diseased children showed that, in the various forms of respiratory derangements studied, the most constant change noted was an increase in the FRC/TLC ratio. This ratio differs markedly from the constant value obtained in the normals making it a useful value in following the progress of chronic lung involvement. Although the ratio is outside the range of

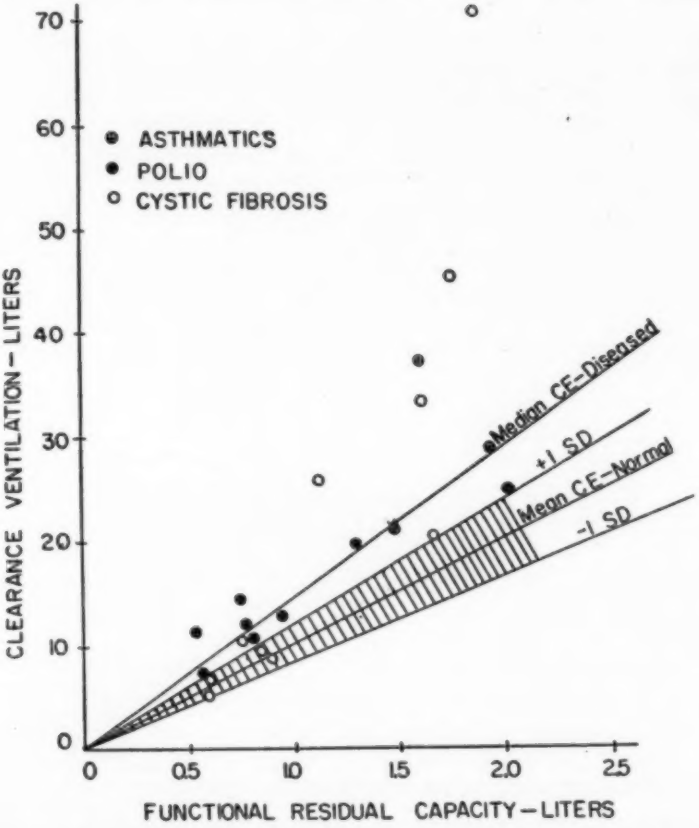

FIGURE 2: Relation between clearance ventilation and functional residual capacity in twenty-one diseased children. The graph also shows the mean and standard deviations of the normal series contrasted with the median of the diseased children.

normal in each type of pathology, the variation in the different compartments is not the same. In asthmatics, the FRC is characteristically enlarged with a reduction of IC, thereby elevating the ratio. In contrast, the post-paralytic polio patients showed a small FRC with a more marked diminution in TLC. This is in agreement with findings in adult poliomyelitis patients in whom a reduction in FRC and TLC[14] and loss of compliance has been reported.[15,16] Changes in cystic fibrosis of the pancreas parallel those in polio, but are probably due to chronic scarring and fibrosis with loss of elasticity of the lung tissue.

Consideration of intrapulmonary gas mixing in the diseased children indicates derangement of mixing in all types of chronic respiratory disease studied. Figure 2 shows that the median clearance equivalent of these children lies well above one standard deviation of the mean of the normal group. This would indicate that disturbances in intrapulmonary gas mixing are a frequent finding in diseases of this type.

Use in Clinical Evaluation: To illustrate the use of these determinations in clinical evaluation, the results obtained on the largest group, ten children with cystic fibrosis of the pancreas, are discussed.

In Table 5 the children with cystic fibrosis of the pancreas are graded on the basis of clinical and x-ray severity of lung pathology. Grade I designates children who have no signs or symptoms of pulmonary involvement and a normal chest x-ray film. Grade II designates children with minimal clinical manifestations such as fatigue at the end of the day, increased susceptibility to respiratory infection and only occasional exacerbations of pulmonary infection. Their chest x-ray films indicated only minimal changes consistent with fibrosis and emphysema. Grade III designates children who have moderate signs and symptoms of pulmonary disease including shortness of breath, occasional cyanosis, fatigability, and more or less chronic pulmonary infection. Chest x-ray films of these children showed signs of some emphysema and only moderate evidence of pulmonary fibrosis, Grade IV designates children with signs and symptoms of severe pulmonary disease such as chronic cyanosis with polycythemia, clubbing of the digits, chronic pulmonary infections with acute exacerbations, and severe reduction of physical activity. Pulmonary changes on x-ray films show evidence of marked emphysema, partial atelectasis, bronchiectasis, and fibrosis.

It is noticed in Table 5 that changes in the clearance equivalent and FRC/TLC ratio parallel closely the changes noted clinically. Often clinical judgment and x-ray findings are not sensitive enough to discover early changes or to determine the

TABLE 4—COMPARISON OF MEDIAN VALUES OF NORMAL AND DISEASED CHILDREN

Physical Characteristics

Subjects	Age. Yr.	Age. Mo.	Height (Ins.)	Weight (Lbs.)	B.S.A. (Sq. M.)	A. P. Dia. (Ins.)	Circ. (Ins.)
Normal N=50	9	0	54.5	74	1.11	5.8	26.0
Asthmatics N=3	10	0	51.0	63	1.01	6.5	27.0
Post Paralytic Polio N=8	9	7	53.0	50	.94	4.7	22.0*
C/F N=10	7	4	47.7	46	.84	5.7	23.5

Lung Volumes

Subjects	I.C. (Liters)	E.R.V. (Liters)	V.C. (Liters)	F.R.C. (Liters)	T.L.C. (Liters)	F.R.C. T.L.C.	F	T.V. (Liters)	M.V. (Liters)
Normal	1.62	.38	2.05	1.18	2.83	.417	18	.45	8.2
Asthmatics	1.35	.46	1.83	1.80	3.13	.522	18	.39	7.0
Post Paralytic Polio	.70	.25	.82	.79	1.47	.511	20	.36	6.7
C/F	.63	.10	.72	1.02	1.93	.561	26	.29	7.8

Intrapulmonary Gas Mixing

Subjects	Clr. Vent. (Liters)	Clr. Eqv.	F	T.V. (Liters)	M.V. (Liters)
Normal	13.6	11.3	18	.61	11.4
Asthmatics	29.1	15.2	20	.52	10.3
Post Paralytic Polio	12.9	14.9	21	.56	11.2
C/F	15.4	18.1	25	.37	10.6

*Mean Value

TABLE 5—CHANGES IN CLEARANCE EQUIVALENT AND FRC/TLC RATIO IN CYSTIC FIBROSIS OF THE PANCREAS

Grade	Mean Clr. Eqv.	Mean FRC/TLC
I	11.4	.475
II	12.2	.556
III	25.5	.590
IV	32.4	.743

severity of the impairment present. For these reasons clearance equivalent may be helpful in evaluation of the disease process, determination of proper therapy, and estimation of a prognosis.

The observations discussed above portray some important aspects of pulmonary ventilatory efficiency at any one moment. However, a greater value may lie in their use for serial evaluation during the course of the natural history of a disease. Figure 4 represents five serial determinations of the clearance equivalent for one of the cystic fibrosis patients obtained during the terminal eight months of her life. A brief summary of this child's clinical history is included here:

S. S., a ten-year-old, white girl, deceased February, 1959, was first seen at nine months of age for an intestinal obstruction and a chronic upper respiratory infection. A fat free diet with pancreatic supplement and antibiotics was prescribed. The diagnosis was later confirmed as cystic fibrosis of the pancreas. She had six hospital admissions over a period of five years for exacerbations of pneumonitis. X-ray findings

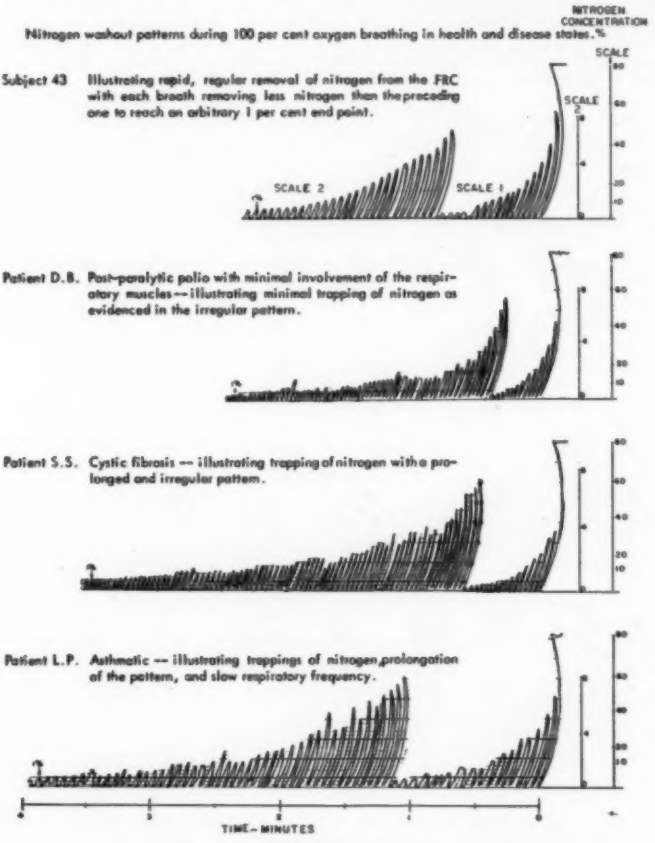
NITROGEN CONCENTRATION %
Nitrogen washout patterns during 100 per cent oxygen breathing in health and disease states.
Subject 43 Illustrating rapid, regular removal of nitrogen from the FRC with each breath removing less nitrogen than the preceding one to reach an arbitrary 1 per cent end point.
SCALE
SCALE 2
SCALE 1
Patient D.B. Post-paralytic polio with minimal involvement of the respiratory muscles -- illustrating minimal trapping of nitrogen as evidenced in the irregular pattern.
Patient S.S. Cystic fibrosis -- illustrating trapping of nitrogen with a prolonged and irregular pattern.
Patient L.P. Asthmatic -- illustrating trappings of nitrogen, prolongation of the pattern, and slow respiratory frequency.
TIME - MINUTES

FIGURE 3

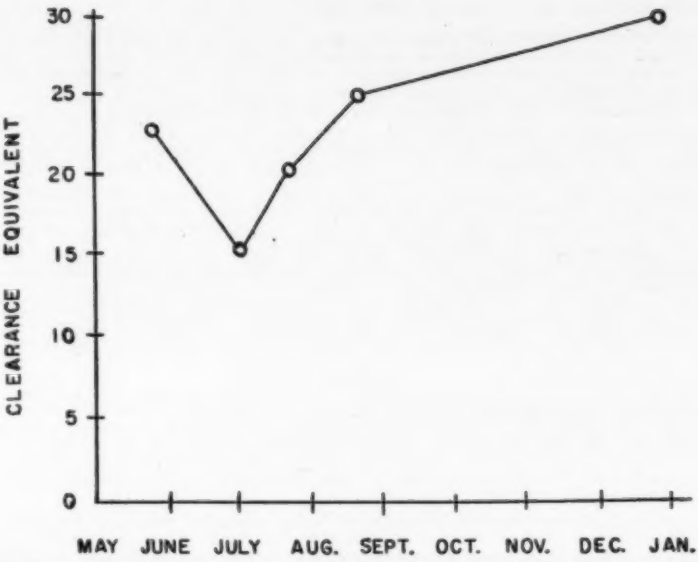

FIGURE 4: Changes in clearance equivalent during the terminal eight months of life in cystic fibrosis of the pancreas patient, S. S.

initially indicated diffuse bronchopneumonia which progressed to a diffuse bilateral scarring with marked emphysema, enlargement of the thoracic compartment, and increased density of the hilar markings. At the time of her last admission she showed intermittent cyanosis with clubbing of the digits, marked retardation of growth and development, obvious hyperinflation of the thorax, and sibilant and sonorous rales scattered over both lung fields.

The initial determination, as depicted in Figure 4, was done prior to her seventh hospital admission where a regime of postural drainage, breathing exercises, and intermittent positive pressure breathing with an antibiotic-detergent aerosol was carried out. The second determination was done following release from the hospital. The third and fourth determinations were done when the patient returned to the outpatient clinic. The fifth determination was done immediately prior to the child's last admission and death. The clearance equivalent was most abnormal at this time.

SUMMARY

Clinical evaluation of respiratory status in chronic diseases of childhood depends upon: (1) the use of meaningful values which accurately portray pathophysiological changes and which may be determined with relative ease; (2) determination of adequate baseline values on normal subjects to which the finding in disease may be compared; and (3) the use of serial determinations throughout the natural history of the disease.

In this study lung volumes and intrapulmonary gas mixing values determined in the supine position in 50 normal children are compared to those of 21 children with asthma, post-paralytic polio, or cystic fibrosis of the pancreas. Inspiratory capacity, expiratory reserve volume and vital capacity were determined by spirometry. The functional residual capacity was determined by an open circuit nitrogen dilution technique. Gas mixing efficiency as defined by the clearance equivalent was also determined.

On the basis of this study it may be concluded that changes in lung volumes, intervolume ratios, and intrapulmonary gas mixing may be used to evaluate clinical changes in chronic pulmonary diseases of childhood and that serial determinations give added significance to these studies.

ACKNOWLEDGEMENT: The authors are indebted to Doctors William A. Spencer, Carlos Vallbona, Robert R. Jackson, Gunyon M. Harrison, James Alexander, and Daniel Jenkins for their guidance and clinical judgments; to Richard Craddock for his technical assistance; and to Miss Patsy Kimball and Mrs. Elena Hurst for their help in typing and multilithing the paper.

RESUMEN

La estimación clínica de las condiciones respiratorias en las enfermedades crónicas de la infancia, dependen de: (1) el uso de valores significativos que reflejan exactamente los cambios fisopatológicos y que será de fácil uso, (2) la determinación de los valores básicos normales con los que puedan compararse los patológicos; y (3) el uso de determinaciones en serie a través de la evolución de la enfermedad.

En este estudio se determinaron los volúmenes gaseosos de la mezclas intrapulmonares en posición supina en 50 niños normales y se compararon con los de 21 niños con asma, polio postparalítica, o enfermedad fibroquística del páncreas.

La capacidad inspiratoria, el volumen de la reserva expiratoria y la capacidad vital, se determinaron por espirometría. La capacidad funcional residual se determinó por método del circuito abierto con dilución de nitrógeno. Se determinó la eficiencia de la mezcla de los gases por el equivalente de la dilución.

Basándose en este estudio, puede concluirse que los cambios en los volúmenes pulmonares las relaciones entre ellos y las mezclas de los gases intrapulmonares, pueden servir para estimar los cambios clínicos en las enfermedades crónicas de la infancia y que las determinaciones en serie proporcionan una significación adicional a estos estudios.

RESUMÉ

L'estimation clinique de l'état respiratoire dans les affections chroniques de l'enfance dépend de: (1) l'emploi de valeurs significatives qui donnent un tableau précis des altérations physio-pathologiques et qui peuvent être déterminées relativement facilement; (2) la détermination de valeurs de référence convenables en comparant les sujets normaux avec ceux qui sont atteints par la maladie; (3) l'emploi de mesures en série faites au cours de l'histoire de l'affection.

Dans cette étude, les volumes pulmonaires et les valeurs de mélange des gaz intrapulmonaires déterminées en position déclive sont comparées chez 50 enfants normaux à ceux de 21 enfants atteints d'asthme, de paralysie post-poliomyélitique ou de fibrose kystique du pancréas. La capacité inspiratoire, le volume d'air de réserve et la capacité vitale furent déterminées par spirométrie. La capacité fonctionnelle résiduelle fut déterminée par une technique de dilution de l'azote en circuit ouvert. L'efficacité du mélange gazeux, comme il est défini par l'équivalence de clearance, fut également déterminé.

D'après cette étude, on peut arriver à la conclusion que les altérations des volumes pulmonaires, les quotients inter-volume et le mélange des gaz intrapulmonaire peuvent être utilisés pour évaluer les altérations cliniques dans les affections pulmonaires chroniques de l'enfance et que des déterminations faites en série donnent une signification accrue à ces études.

ZUSAMMENFASUNG

Die klinische Auswertung des Zustandes des Respirationssystems bei chronischen Krankheiten im Kindesalter hängt ab von: (1) Der Verwendung von Werten von Bedeutung, die genau die pathophysiologischen Veränderungen wiedergeben und diese relativ einfach ermitteln lassen; (2) von der Festlegung von adäquaten Ausgangswerten an normalen Fällen, mit denen die Resultate von Kranken verglichen werden können; (3) von der Durchführung serienmässiger Messungen während des gesamten Krankheitsablaufes.

Bei der vorgelegten Untersuchung werden die Werte der Lungenvolumina und des intrapulmonalen Gasaustausches, wie sie bei 50 normalen Kindern in Rückenlage ermittelt wurden, verglichen mit solchen von 21 Kindern mit Asthma, postparalytischer Poliomyelitis oder cystischer Pankreasfibrose. Die Insiprationsluft, das expiratorische Reservevolumen und die Vitalkapazität wurden spirometrisch erhoben. Die funktionelle Residualluft furde mit der Technik der offen zirkulierenden Stickstofflösung bestimmt. Der Wirkungsgrad des Gasaustausches, definiert durch den clearance-Äquivalenten wurden ebenfalls gemessen.

Von den Ergebnissen dieser Untersuchungen ausgehend kann gefolgert werden, daβ Abweichungen in den Lungenvolumina, im Verhältnis der Volumenwerte zueinander und der intrapulmonale Gasaustausch sich verwenden lassen zur Ermittlung klinischer Veränderungen bei chronischen Lungenkrankheiten der Kindheit, und daβ serienmässige Bestimmungen diesen Untersuchen eine erhöhte Bedeutung verleihen.

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AORTOGRAPHY IN THE DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS

The diagnosis of patent ductus arteriosus is best made with thoracic aortography. The trans-carotid method of injection of the opaque dye through a wide metal catheter pushed into the ascending branch of the aorta has advantages to recommend it. This method of aortography was used in 24 patients, in 21 cases for diagnosing patent ductus. Two films are taken 3-4 seconds after injecting the dye, using the ordinary x-ray machine. Simultaneous filling of the aorta and the pulmonary artery and early filling of the left half of the heart serve as a direct indication of the existence of patent ductus arteriosus. All patients stood the investigation well and 18 of them have been successfully operated. With due care, the trans-carotid aortography is a harmless method of investigation.

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Combined Therapy of Inoperable Lung Carcinoma with 5-Fluorouracil and Irradiation*,**,†

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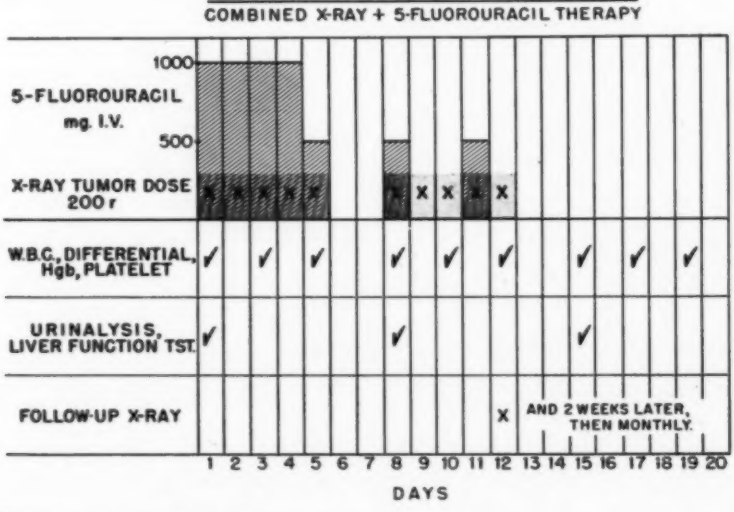
The treatment of patients with inoperable carcinoma of the lung has been discouraging and unsatisfactory. X-ray therapy offers but little help in such cases, even with the newer "supervoltage" and rotational techniques. The search for chemical compounds of greater effectiveness in this disease than nitrogen mustard has proved equally unrewarding to date. We have recently completed a preliminary study of the treatment of lung carcinoma by the simultaneous administration of orthovolt x-ray and a fluorinated pyrimidine, 5-fluorouracil.

5-fluorouracil has had extensive trial in a variety of malignancies[1-4] and, even in toxic doses, has proved completely ineffective in pulmonary carcinoma. However, recent studies[5,6] have suggested that this compound might potentiate the anti-tumor effect of radiotherapy and our findings in the treatment of carcinoma of the lung are of special interest in this respect.

Method of Treatment

X-irradiation was administered at 250 Kv.,hvl 3 mm.cu., in daily tumor doses of 100-200 roentgens, five days a week, to a total tumor dose of 2000r.

TABLE 1—SCHEDULE OF CONCURRENT X-RAY AND 5-FLUOROURACIL ADMINISTRATION


PLAN OF TREATMENT AND STUDY
COMBINED X-RAY + 5-FLUOROURACIL THERAPY
1000
5-FLUOROURACIL
mg. I.V.
500
X-RAY TUMOR DOSE
200 r
W.B.C., DIFFERENTIAL, Hgb, PLATELET
URINALYSIS, LIVER FUNCTION TST.
FOLLOW-UP X-RAY
AND 2 WEEKS LATER, THEN MONTHLY.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
DAYS

*From the Veterans Administration Hospital.

**The essentials of this study were presented at the 26th Annual meeting, American College of Chest Physicians, Miami Beach, Florida, June 8-12, 1960.

†5-Fluorouracil was generously supplied by Hoffman-LaRoche, Inc., Nutley, New Jersey.

5-fluorouracil was given intravenously over a two to three hour period, in 200-500 cc. of normal saline, starting on the first day of x-ray therapy and continuing until such therapy had been completed. The dosage schedule was as follows:

Days 1 through 4: 15 mg./kg. (not more than 1000 mg./day)

Day 5 and twice weekly thereafter: 7.5 mg./kg. (not more than 500 mg./day)

The usual course of combined therapy required two weeks, during which time the patient received approximately 90 mg./kg. of 5-fluorouracil.

To date we have treated and evaluated 16 patients with inoperable, biopsy proved, epidermoid carcinoma of the lung. In each, the tumor was measurable objectively by x-ray or palpation.

The following studies were performed on every patient: white blood cell count, differential, hemoglobin and platelet count three times weekly; reticulocyte count, urinalysis, serum albumin, globulin, uric acid and alkaline phosphatase once weekly. The patients were examined daily for evidence of toxicity. The response of the malignancy to combined therapy was measured on the last day of treatment and every two weeks thereafter.

Toxicity

Five of the 16 patients experienced no toxicity whatsoever. Of the remaining 11, seven had moderately severe pharyngitis or esophagitis, involving, in each instance, areas within the field of irradiation. Four developed leucopenia below 3000 cells/cu.mm. and four thrombocytopenia below 100,000 cells/cu.mm. Toxic manifestations were transient, disappearing within seven to 10 days upon cessation of therapy. In no case did toxicity prevent completion of the therapeutic program and there was no death in this series.

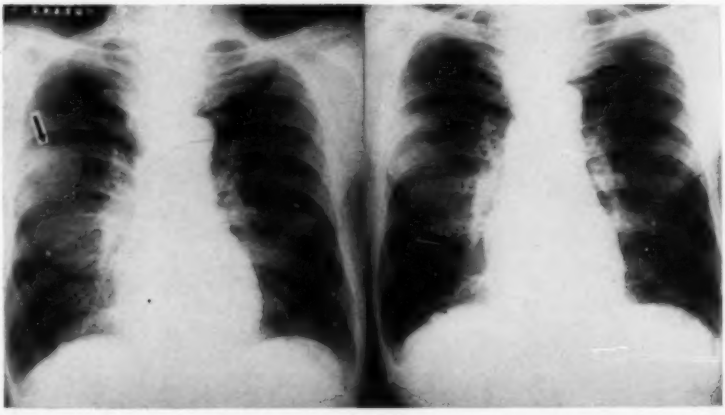


FIGURE 1: A 64-year-old man, discovered on routine chest x-ray film to have a large ovoid mass in the right upper lobe. An exploratory thoracotomy proved the lesion inoperable because of extension to the mediastinum. Biopsy diagnosis: epidermoid carcinoma of the lung. He was treated with x-ray and concurrent 5-fluorouracil from February 24, 1959 to March 9, 1959. Two weeks later (March 23, 1959) a repeat chest x-ray film showed marked reduction in the size of the mass.

Results

In each of the 16 patients there occurred unequivocal regression of the treated tumor masses within two weeks of completion of simultaneous x-ray and 5-fluorouracil therapy.

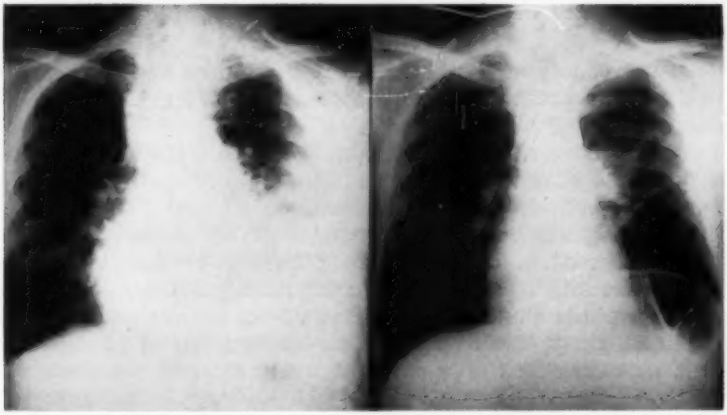


FIGURE 2: A 70-year-old man with a 30 pound weight loss, superior vena caval syndrome and severe pain in the left arm of 3 months duration. There was a huge, hard, fixed left supraclavicular mass. A chest x-ray film on April 9, 1959 showed lobulated mediastinal and hilar masses, a dense infiltrate in the left lower lobe and a left pleural effusion. Biopsy diagnosis: epidermoid carcinoma of lung. He was treated from April 20, 1959 to May 5, 1959 with 5-fluorouracil and 2000 r. x-irradiation through both a mediastinal and a supraclavicular port. On May 19, 1959, there was marked regression of the tumor masses, left lower lobe infiltrate and pleural effusion. The superior vena caval syndrome and left arm pain had disappeared. He subsequently demonstrated complete clearing of the chest x-ray film, regained 30 pounds and, one year later, was active, without complaints or evidence of tumor.

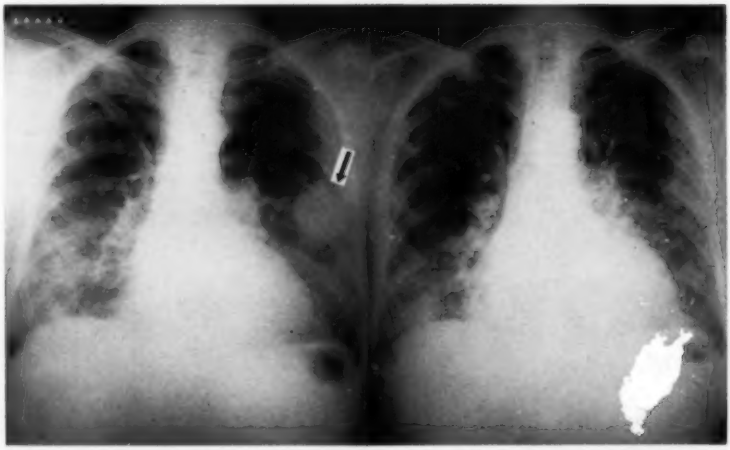


FIGURE 3: A 69-year-old man, hospitalized for treatment of decompensated arteriosclerotic heart disease. A routine chest x-ray film showed a large round mass in the left upper lobe. Biopsy diagnosis: epidermoid carcinoma of the lung. He received combined x-ray and 5-fluorouracil therapy from September 14, 1959 to September 25, 1959. Two weeks later (October 9, 1959) there was marked diminution in the size of the mass which subsequently completely disappeared. The patient expired on October 20, 1959 of a staphylococcal bronchopneumonia.

Since we selected cases with only the most advanced and widespread disease for this preliminary study and treated only those lesions that were objectively measurable, we did not expect to alter significantly the fatal course of the disease in these patients. However, several of them are alive and comfortable six months after combined therapy. One of these, considered terminal when treatment was undertaken, was, 12 months later, ambulatory and symptom-free.

"Before and after" roentgenograms of three illustrative cases are presented below. In each pair of films, the one on the right was taken two weeks after the completion of combined therapy. In most of our cases, there was even further improvement during the ensuing months.

SUMMARY

Sixteen patients with inoperable epidermoid carcinoma of the lung were treated with local orthovoltage x-ray to a tumor dose of 2000 roentgens while receiving 5-fluorouracil. The course of combined therapy required two weeks for completion.

Toxicity occurred in 11 of 16 patients and included leucopenia, thrombocytopenia, esophagitis and pharyngitis.

Marked and rapid regression of the treated tumor mass was observed in every patient.

The simultaneous administration of low dosage x-ray and 5-fluorouracil appears to be highly effective in the treatment of epidermoid carcinoma of the lung. Further study of this, and other similar therapeutic combinations, may materially improve the otherwise dismal prognosis of patients with this disease.

RESUMEN

Se trataron dieciseis enferoms de cancer epidermoide del pulmón inoperables usando rayos X por terapia de ortovoltaje local a la dosis tumor de 2000 roentgens al mismo tiempo que recibieron 5-fluororacil. La serie del tratamiento requirió dos semanas.

Se notó toxicidad en 11 de los 16 enfermos incluyendo: leucopenia, trombocitopenia, esofagitis y faringitis.

Se notó una marcada y rápida regresión de las masas tumorales trttadas en todas los enfermos.

Parece que la administración simultánea de rayos X de baja dosificación y el 5-fluoracil es altamente efectiva en el tratamiento del cancer epidermoide del pulmón. El estudio ulterior de esta y de otras combinaciones terapeuticas similares puede materialmente mejorar el pronóstico de esta enfermedad que de otro modo es desalentador.

ZUSAMMENFASSUNG

Es wurden 16 Kranke mit inoperabelem Epidermoid-Carzinom der Lunge lokal behandelt mit Ortho-Volt-Röntgenstrahlen in einer Tumordosis von 2000 r bei gleichzeitiger Gabe von 5-Fluorouracil. Der kombinierte Behandlungsverlauf erforderte zu seiner vollständigen Durchführung 2 Wochen.

Toxische Erscheinungen traten bei 11 von 16 Patienten auf, nämlich Leukopenie, Thrombozytopenie, Oesophagitis und Pharyngitis.

Bei jedem Kranken kam es zu einer ausgesprochenen und raschen Rückbildung der behandelten Tumormasse.

Der gleichzeitige Einsatz von Röntgenstrahlen in niedriger Dosis und von 5-Fluorouracil scheint von starker Wirksamkeit zu sein bei der Behandlung von Epidermoid-Carzinom der Lunge. Weitere Beobachtungen mit dieser und anderen ähnlichen therapeutischen Kombinationen kann die sonst ungünstige Prognose von Patienten mit dieser Erkrankung wesentlich verbessern.

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Tuberculosis and Asthmatic Bronchitis in Sarcoidosis

Some Observations on 150 Cases of Besnier-Boeck-Schaumann Disease

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SILTZBACH (1957): "For most investigators, delving into sarcoidosis has been like working in a dark room, but recently some light has been seeping in as if through a crack in the door. When that door will finally be fully opened, none can even vaguely guess."

Introduction

The overall picture of sarcoidosis is well known and has been described during the past decade in several monographs (Longscope, Leitner, Turiaf, Heilmeyer-Wurm-Reindell) and long articles (Lofgren, Scadding, Israel, Zettergren).

Our investigation consisted of the systematical analysis of the data obtained from the hospital and out-patient examination of 150 cases of Besnier-Boeck-Schaumann disease (B.B.S.) mainly observed between 1951 and 1956. In addition, another 60 cases were studied to obtain a greater amount of comparable material; for some part these were recent B.B.S. cases from the clinic (52), for another part (8) cases from the literature (Van Buchem). Our personal investigation therefore concerned 202 patients.

Only selected data are presented; a complete survey is given in the academical thesis of one of us (ten Have). The same holds for the literature.

Methods

The clinical examination was carried out according to the traditional lines: past history, physical examination, laboratory procedures (including urine analysis, blood pictures, sputum analysis according to Mulder (Mulder, Orie), tuberculin reactions, x-ray examination (often including tomographic and bronchographic examinations).

Pathological examination was mostly done on a speciment obtained by:

a. supraclavicular biopsy of Daniels, which was carried out 109 times (81 per cent positive),
b. liver biopsy, carried out 54 times (61 per cent positive).

Nothing is said about the Kveim reaction, the tuberculin neutralization and BCG tests, as the data concerning these tests, largely obtained from the same patients, have already appeared in another publication (Beaumont, 1957).

The findings in the pulmonary function examinations will be published *in extenso* in a separate study (Witkop, in preparation). The latter have been used in assessing the "asthmatic condition" prevalent in some of the patients.

(Supported by grants from the National Research Council T.N.O. and the Tuberculosis Research Council [K.N.C.V.])
From the Division of Pulmonary Diseases (Prof. Dr. N. G. M. Orie) and the Medical Department (Prof. Dr. F. S. P. van Buchem) of the State University, Gronigen, Netherlands.

Material

The 150 cases were devided into three groups, acccording to the tuberculin reactions and the pathological-anatomical findings.[1]

Group I:

"Classical" cases (81) demonstrated a clinical (including roentgenological) picture of B.B.S. with a pathological-anatomical picture of epitheloid cell granulomas without necrosis[2] and negative Pirquet and Mantoux 1/1000 reactions.

Group II:

Cases with a clinical picture of B.B.S. (47), the pathological-anatomical substrate of which showed epitheloid cell granulomas without or with only slight necrosis, while the tuberculin reactions were weakly positive or alternatingly positive and negative.

Group III:

Clinically manifest cases of B.B.S. (22), in 19 patients the biopsy did not lend support to the diagnosis, or only insufficient support; no biopsy was carried out in three patients.

This classification was especially intended to find out whether the differences can influence the clinical results, either as regards the course or the prognosis.

For all findings, due attention was given to striking differences between men and women, if any.

The 150 cases were divided as follows:

		Women	Men
Total	150	71	79
Group I	81	34	47
Group II	47	25	22
Group III	22	12	10
Average age: women 41 years, men 34 years.			

It should be emphasized that these 150 cases were only a small part of the 700 cases observed during the same period (1951-1956) in the Northern Provinces of The Netherlands.

This implies that both the greatly varying symptom complex and the findings of the physical, laboratory and x-ray film examinations cannot be regarded in all respects as representing an average picture of B.B.S. They were the more severe and/or protracted cases.

History

Some particulars from the anamnesis are found in the thesis of one of us (ten Have), about social conditions, about five cases of familial occurrence. Seventy-four per cent of the patients had complaints for which they had consulted a doctor.

The percentage of complaints presumably originating in the central nervous system is remarkably high. In a number of cases, pain in the left shoulder was an outstanding symptom. These patients usually suf-

[1]Results of the morbid-anatomical examination: in 75 per cent of the cases (112/150) epitheloid cell granulomata without necrosis were found. Fourteen showed more or less deviating findings.

[2]Of two patients the pathological-anatomical substrate was not known, but both had cutaneous changes in the form of unmistakable Boeck's sarcoids.

fered from splenomegaly. This perhaps suggests that in case of vague complaints in the left shoulder, the possibility of an existing B.B.S. with involvement of the spleen should be taken into consideration.

Tuberculosis

The first fact which struck our attention was the high number of cases in which tuberculosis was found in the family history: 34 per cent in men as well as in women (34.2 - 33.8).

Group I—34.5 per cent, Group II—42.5 per cent, and Group III—13.6 per cent.

These figures only refer to the cases of which could be assumed with *certainty* that they had been in *close* contact with *open* tuberculosis. Fourteen cases in which this was more or less dubious were left out of consideration. Tubercle bacilli were demonstrated in 11 patients during the period of observation; four of them are not included in the 34 per cent mentioned.

The frequency of calcifications in our series is shown in the following table:

		Group I	Group II	Group III
Manifest	14 (9 per cent)	5 (6 per cent)	8 (17 per cent)	1
Dubious	21 (14 per cent)	9 (11 per cent)	9 (19 per cent)	3 (13 per cent)

Of the 14 patients with manifest calcifications, eight were not included in the above mentioned 34 per cent, as were 15 of the 21 with dubious calcification foci.[1]

The frequency of a tuberculosis-positive past history in our series is therefore undoubtedly higher than 34 per cent.

	certain contact with tbc patients	34 per cent
	tubercle bacilli 4/150	2.6 per cent
positive anamnesis		36.6 per cent
	manifest calcium	5.3 per cent
		41.9 per cent
± anamnesis	dubious contact with tbc pat. 14/150	9.3 per cent
	dubious calcium	10 per cent
		61.2 per cent

Baas and Van Voorst Vader found an incidence of 36 per cent of 128 B.B.S. patients, Smellie and Hoyle found 48 per cent of 60 B.B.S. patients.

These frequencies are undoubtedly high, and are for example comparable with the figures given for active tuberculosis.

In the five-year period 1952-1956, a total of 52,646 cases of tuberculosis were examined in the Netherlands, including the relapses. The source of infection was known in only 30 per cent.[2]

[1]Address presented to the "Dutch Association for the Study of Pulmonary Diseases and Tuberculosis" by Professor Dr. P. Muntendam on April 25, 1958 at Utrecht, upon the occasion of the 50th anniversary of this association.

[2]The reason to consider most of the pulmonary calcifications in The Netherlands as resulting from tuberculosis have been published earlier (Orie and De Groof, 1952).

Frequency of Complicating Asthma or Asthmatic Bronchitis

A second important anamnestic item is the frequent occurrence of asthmatic and other "allergic" conditions both in the patient and his family.[1]

The total number of cases with "positive allergy" is 49/150=33 per cent (group I—29.6 per cent, group II—38 per cent, and group III—31.8 per cent).

The additional number of cases with ± allergy is 7/150=5 per cent.

We must keep in mind the possibility that these figures have undergone some influence by selection. Our patients were selected, usually on the basis of their complaints and persisting or extensive changes. More than half of them (80/150=53 per cent) were radiologically in a far advanced stage, often with widespread localizations.

Even then, however, the remarkable correlation remains between protracted diseases and asthmatic (bronchitic) pre-existent history.

Interesting data are obtained by comparing the data of the "allergic" history with the results of the radiological and functional examination.[2]

Roentgenology

Three stages of development were distinguished in the pulmonary x-ray picture. Of 146 patients[3] (68 women, 78 men) 49 (23 women) had only glandular enlargement (first stage), and 68 (31 women) only peripheral lesions (third stage).

Mass screening at the chest clinics shows quite different data for the ratio between glandular enlargements and peripheral lesions: from 344 patients (277 women, 117 men), 216 (153 women) showed first and only 35 third stage.

The above figures therefore clearly demonstrate the selectness of our material. This leads to remarkable consequences. While mass screening shows a marked predominance of women B.B.S. patients, there is no question of any such predominance in our series. On the contrary, the men even form a small majority, in particular in the classical group.

Wurm demonstrates in a table that as B.B.S. advances toward the stage of fibrosis, the percentage of women shows a striking decrease. This agrees with our experiences. Wurm is of the opinion that hormonal factors exert an influence in this respect. We often see a concurrence with "allergic" factors (two views which do not exclude each other, however). We have already mentioned the total percentage of "positive al-

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[1]Under "asthmatic conditions" we understand *paroxysmal bronchial asthma as well as asthmatic eosinophilic bronchitis* (the characteristics of which have been described in another publication: Orie 1958) pre-existent to B.B.S. usually combined with an "allergic" past history of patient and/or his family. Under "allergic anamnesis" we understand affections preceding B.B.S., like hay-fever, infantile eczema, asthma, asthmatic bronchitis in the patient himself or in his nearest family (father, mother, brothers, sisters, children). We call this a "positive allergic anamnesis" (pos. all.). In addition, sinusitis, nasal polyps and a possible combination of signs and symptoms like attacks of rhinorrhoea, frequent colds, frequent pneumonias in the youth, are regarded as a manifestation of one and the same affection, but here indicated with±. During the examination for B.B.S., "allergic" phenomena may become manifest (blood and sputum eosinophillia, adrenaline-histamine effects in the examination of the pulmonary function) in patients whose past history shows nothing or only very little of "allergy." In our series this was the case with 6 patients.

[2]Pulmonary function.

[3]146, not 150, because in four patients the changes on the first x-ray film were too slight to warrant a diagnosis.

lergy": 33 per cent. For women this is 24 per cent, for men 40.5 per cent. Per stage the figures are: first stage 14.2 per cent, second stage 19.4 per cent, third stage 43.7 per cent.

The "asthma" component is therefore nearly twice as great in the men as in the women, and is especially manifest in the third stage.

The question arises as to what should be considered primary: the asthma factor of B.B.S. In view of the high number of cases (30 of the 49) with "allergic" manifestations in the early personal or family history of the patient, it does not seem improbable that the "allergic" factor is primary, and one wonders whether when an M.B.B.S. does not run the classical favourable course, this should be attributed to a concomitant asthmatic constitution and (or) sputum infection (or possibly also to a pre-existent tuberculosis), and whether this is the cause of the gross-patchy appearance in the third stage.

Calcification

In four patients[1] calcium deposition was demonstrated radiologically during the course of the disease.

Laboratory examinations

Results of blood and urine analysis are not given in detail; neither are they given for serum proteins.[1]

Sputum examination

Compared with other pulmonary diseases (asthma, emphysema), remarkably few infections of the respiratory passages were found in B.B.S.

In 14 per cent of the patients (21, of whom ⅔ "asthma" cases) a bacterial infection of the sputum was found (Table 1).

TABLE 1—BACTERIAL INFECTIONS OF RESPIRATORY TRACT IN 150 PATIENTS WITH BESNIER-BOECK-SCHAUMANN'S DISEASE

	Group I (women 34)	Group I (men 47)	Group II (women 25)	Group II (men 22)	Group III (women 12)	Group III (men 10)	Total percentage
A. No sputum, or only mucus, or little purulent sputum, of which no preparation could be made.	31	33	17	17	10	8	76.6
B. In the course of the disease on one or more occasions purulent sputum, in which no bacteria were demonstrated.	1	4	4	2	1	1	8.6
C. In the course of the disease on one or more occasions purulent sputum with bacteria.	2	10	4	3	1	1	14

This percentage is of course only of relative value, as it is to a high extent dependent on the frequency of examination and on the fact that the infections were usually of an intermittent nature. We believe that

[1]For details see Academical Thesis ten Have.

it is justified to regard a continuous or continually recurring airway infection as a complication, i.e., that it should not be included in the clinical picture of B.B.S. It is probably in the majority of the cases the result of a co-existent chronic eosinophilic (asthmatic) bronchitis ("asthma").

The most important place in the bacterial flora was occupied by *H. influenzae.*

Tuberculin reactions

In 90 of our 150 patients, the reactions remained negative throughout the whole observation period (60 per cent); alternately positive and negative in 50 (33.4 per cent); (first stage 24 per cent, second stage 22 per cent, third stage 37.5 per cent) and continuously positive in 10 patients (6.6 per cent).

Course of the disease

The radiological course of the disease could be studied in 146 patients, in four the changes on the roentgenogram being too slight for a study.

In 33 per cent of cases (48/146) the radiological abnormalities had completely or almost completely disappeared after an average observation time of 26 months. Few differences were found between the first stage (with 40 per cent) and the second stage (with 36 per cent) as regards course and duration (20 and 22 months on an average).

The third stage shows the greatest deviations in an unfavorable sense (18 per cent) after an average observation period of 36 months.

Of the 86 patients in whom the abnormalities did not disappear, 30 (35 per cent) were observed for more than three years.

The radiological examination also revealed certain differences between the three groups, in particular between the classical group (I) and the group with positive or alternating tuberculin reactions (II). The most remarkable feature is the better prognosis of group II.

Sex differences were also clearly demonstrable in the x-ray film examinations. We were primarily struck by the frequency of marked glandular enlargement in the women in the first stage of the classical group as compared with the predominantly moderate glandular swelling among the men. Further differences mainly concerned the peripheral pulmonary changes and the respiratory infections in the third stage, which were predominant among the men (women 16 per cent, men 25.6 per cent). These differences are probably closely related with the differences in prognosis for the two sexes.

In the first stage (glandular enlargement), the percentage of cures is more or less the same in women (39 per cent) and men (42 per cent). In the initial disseminations (stage 2) the men have considerably better chances of recovery (45 per cent) than the women (25 per cent), while in the third stage this is precisely the reverse: cure in women 24 per cent, in men 14 per cent.

It thus seems that the changes are more stubborn in the women, but still generally disappear in the long run, while in a small percentage of the men the disease takes an unfavorable course possibly under the

influence of factors discussed before, asthmatic constitution and possibly tuberculosis contact.

The differences found with respect to the course of the various forms, are also remarkable. In the cases with iridocyclitis and in those with skin lesions, the course was often protracted and the prognosis poor. In cases with erythema nodosum, however, the prognosis was particularly good.

Prognosis

Our investigation has shown that in the group of 700 cases detected by the chest clinics from which our series was selected, the chance of fibrosis is 6 to 10 per cent, a group which forms 40 per cent of our patient material. Thanks to our present technique and treatment with ACTH and especially with corticosteroids this percentage is approximately halved.

These results may perhaps even be improved by earlier, longer and possibly more intense treatment, (Roosenburg).

Fourteen patients (9 per cent) of our series died. The mortality rate for the whole group is therefore presumably 2 per cent.

SUMMARY

The most remarkable features in our group of 150 patients with sarcoidosis selected on the basis of severity from ±700 patients observed during the same period in the same region were the following:

1. The high frequency of contact with open tuberculosis.
2. The calcification during the course of the disease.
3. The high frequency of asthmatic-bronchitis (asthmatic constitution) in cases with diffuse long-standing lesions of the third stage (43.7 per cent). This constitution seems to be partly responsible for the signs and symptoms and perhaps also for the chronic course of the disease in these patients and probably explains why in the severe diffuse cases men are predominant over women, the latter having a high frequency in the glandular type.
4. The relatively low frequency of infections of the respiratory passages (14 per cent). These are also largely found in the cases with a history of symptoms and an asthmatic constitution.
5. The favorable effect of the therapy with ACTH and corticosteroids both on the "asthmatic" factor and on the anatomical changes.
6. The occurrence of serious sequelae in 6 to 10 per cent of cases and mortality rate of 2 per cent (overall figure calculated on the 700 cases from which ours were selected).
7. The unfavorable prognosis in the cases with iridocyclitis.

RESUMEN

Las características mas notables de nuestro grupo de 150 (202) enfermos de sarcoidosis seleccionados por su severidad de 700 enfermos aproximadamente observados durante el mismo período en la misma regulón, fueron las siguientes:

1. La alta frecuencia de contacto con tuberculosis abierta.
2. La calcificación en el curso de la enfermedad.
3. La elevada frecuencia de bronquitis asmática (constitución asmática) en casos de lesiones difusas de larga duración en la tercera etapa. (43.7 por ciento).
Esta constitución parece responsable en parte de los síntomas y signos y probablemente de la evolución crónica de la enfermedad y probablemente explica por qué en los casos severos difusos predomina en los hombres sobre las mujeres, siendo en éstas de tipo glandular más frecuentemente.
4. La relativamente baja frecuencia de las infecciones en las vías respiratorias (14 por ciento). Estas son principalmente encontradas en los casos con antecedentes y síntomas de constitución asmática.
5. El efecto favorable del tratamiento con ACTH y corticosteroides tanto sobre el factor "asmático" como sobre los cambios anatómicos.
6. La ocurrencia de secuelas serias en 6-10 por ciento de los casos y la mortalidad de 2 por ciento (número total calculado de los 700 casos de los cuales se seleccionaron los nuestros).
7. El pronóstico desfavorable en los casos con iridociclitis.

RESUMÉ

Les caractéristiques les plus remarquables d'un groupe de 150 malades atteints de sarcoïdose, choisis à cause de la gravité de leur atteinte parmi 700 malades examinés pendant la même période, dans la même région, furent les suivantes:

1. La fréquence élevée d'un contact avec un tuberculeux évolutif;
2. L'apparition de calcifications pendant l'évolution de l'affection;
3. La fréquence élevée de bronchite asthmatique (constitution asthmatique) dans les cas atteints de lésions diffuses du troisième stade persistant depuis longtemps (43.7%). Cette constitution semble être partiellement responsable des signes et symptômes et peut-être également de l'évolution chronique de l'affection chez ces malades, et explique probablement pourquoi dans les cas d'atteinte diffuse grave, les hommes prédominent sur les femmes, ces dernières ayant à plus grande fréquence des atteintes de type glandulaire.
4. La fréquence relativement basse des infections des voies respiratoires (14%). Celles-ci sont également constatées fréquemment dans les cas comportant un antécédent de symptômes et de constitution asthmatiques.
5. L'effet favorable de la thérapeutique par l'ACTH et les corticostéroïdes, à la fois sur le facteur "asthmatique" et sur les altérations anatomiques.
6. L'apparition de séquelles graves dans 6 à 10% des cas et un taux de mortalité de 2% (chiffre moyen calculé sur les 700 cas parmi lesquels les cas des auteurs furent choisis).
7. Le pronostic défavorable dans les cas atteints d'iridocyclite.

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Radiotherapy in Thoracic Neoplasms*

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There is much material available for a statistical evaluation of the current status of radiotherapy in thoracic neoplasms; for primary carcinoma of the lung, six representative reports—three from this country by Leucutia (1958), Schulz (1957), and Leddy (1950), and three from England by Paterson (1950), Hilton (1955), and Brown (1952)—add up to a 2.4 per cent five-year survival rate in 1512 non-resectable cases, which may seem a hardly worthwhile reward from so much effort. But statistics of this kind, although they are the only objective measure we have, do not give a complete picture of the current status of radiotherapy in primary lung cancer; for they refer mostly to patients treated 10 or more years ago, and the last decade has been a period of rising standards and increasing knowledge in radiotherapy, comparable to (and reflecting and incorporating) those in thoracic surgery and general medicine. From another aspect, however, statistics of the results of treatment, whether by surgery or radiotherapy or chemotherapy or combined methods, give too favorable a picture, since the untreated patients are omitted and the size of this untreated fraction is not generally known. It was actually 45 per cent in the Joint Lung Cancer Clinic of the Brompton and Royal Marsden Hospitals in Landon (Bignall, 1958); in the years 1951-55 there were 1749 patients registered and 778 were not treated; of the 971 treated, 35 per cent had surgery, 59 per cent radiotherapy, 5 per cent had surgery followed by radiotherapy, and 1 per cent had preoperative radiotherapy. Churchill (1958) reports that about 35 per cent of the pathologically-confirmed cases are currently resectable, and in this

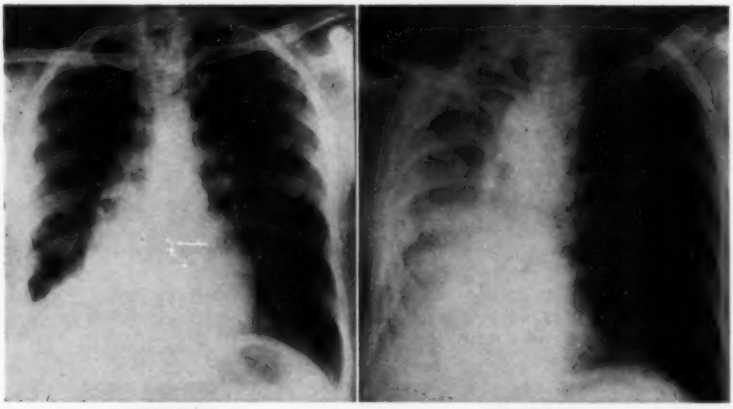

FIGURE 1 FIGURE 2

FIGURE 1 (Case 1): August 1942—anaplastic carcinoma obstructing right lower lobe bronchus. FIGURE 2 (Case 1): August 1956—14 years after 4500 r T.D. Patient well and working.

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resected group the five-year survival rate is 28 per cent. Thus at the present time if there is no improvement in the results of treatment as given five or more years ago, out of 100 pathologically-confirmed and treated cases of primary lung cancer, there will be 10 five-year survivals from surgery and two five-year survivals from radiotherapy; it is my present opinion that this 12 per cent five-year survival rate could even now be doubled.

The various means available for improving the survival rate may be listed as follows:

1. In non-resectable cases, tumor-sterilizing doses of radiation can be safely given by well-planned radioactive implants at the time of thoracotomy, or by the use of supervoltage x-ray and telecobalt with proper dose-planning, or by a combination of the two. It would seem that knowledge of the existence of patients who have been cured of primary lung cancer by radiation alone is very unevenly distributed, so that patients with non-resectable but possibly radio-curable tumors are not given the opportunity of radiotherapeutic consultation or treatment.
2. In resected cases the survival rate of patients with proved metastases in the regional lymph-nodes is only one-third that of patients without lymph-node metastases. Post-operative irradiation of the regional lymph-nodes (or radioactive implants at operation) can improve the salvage rate in this group.
3. About 80 per cent of resected lung cancers show venous invasion, and preliminary studies suggest that many patients have free-floating cancer cells in the blood stream which disappear or decrease in number following irradiation of the primary tumor. The significance of, and the correlation (if any) between venous invasion and free-floating cancer cells in the blood with the incidence of distant metastases and survival rates are yet to be worked out, but it would seem a logical assumption that the use of pre-operative irradiation in selected cases would improve present results.

FIGURE 3 FIGURE 4

FIGURE 3 (Case 2): March 1, 1952—epidermoid carcinoma obstructing right main bronchus. FIGURE 4 (Case 2): Beginning aeration of right upper lobe during course of x-ray therapy.

4. Those lung cancers which give circumscribed shadows radiographically are much more likely to be resectable than the non-circumscribed ones, regardless of the particular cell-type. Since radiation therapy often produces tumor regression with the post-treatment radiograph showing better circumscription of the tumor, more use of pre-operative irradiation would again seem to be a logical step toward improving the survival-rate.
5. Although chemotherapy of lung cancer is not yet by itself a curative treatment, its use in combination with surgery and irradiation in both operable and inoperable cases may well add a further increment to the survival rate. The beneficial effect of the alkylating agents in oat-cell and other undifferentiated carcinomas is widely used, especially for mediastinal compression, and it is also possible that these agents can destroy free-floating cancer cells in the blood and perhaps even tumor emboli before these can become established metastases. The actinomycins have caused the radiographic disappearance of some types of pulmonary metastases and in some cases seem to potentiate the effects of irradiation, so that these agents may also prove useful in primary lung cancer.

Whether or not the wider adoption of these proposals resulted in a higher five-year survival rate, there would certainly be an improvement in the quality of palliation and the duration of symptom-free life, for in general the best palliation is the result of an attempt to cure which fails. The relief of symptoms such as cough, dyspnea, pain, hemoptysis and osteoarthropathy can be obtained by adequate radiation therapy in about 70 per cent of cases, and the disabling effects of metastases in brain or liver can likewise be relieved and so add several months of useful life to the patient.

The following case reports have been selected to illustrate the application of the above suggestions for improving the treatment of primary bronchogenic carcinoma.

Case 1: A 15-year cure by supervoltage x-ray therapy. A man aged 44 was referred to me in 1942 by Dr. Joseph Smart with atelectasis of the right lower lobe (Fig. 1); bronchoscopic biopsy was reported as anaplastic carcinoma, and the tumor was deemed inoperable because of the presence of enlarged hilar lymph nodes. A tumor dose of

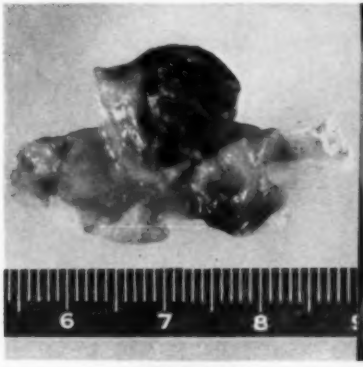

FIGURE 5

FIGURE 6

FIGURE 5 (Case 3): March 20, 1952—plug of tumor tissue expectorated. FIGURE 6 (Case 3): March 26, 1952—aeration of most of right lung; complete relief of symptoms.

4500 r was given in one month to the right chest and mediastinum through opposed large anterior and posterior fields with 1000 kv x-rays, and chest x-rays film in 1956 is reproduced in Fig. 2. He continues in excellent general condition and full work.

Incidentally this case also illustrates the scepticism concerning radiation cures of lung cancer, for the original pathologic slide was lost in 1943 when a land-mine destroyed part of the London Chest Hospital. Dr. Smart told me that when he showed the patient at a clinical meeting in 1954, no one would believe that the patient had indeed had a bronchogenic carcinoma, but fortunately the paraffin block of the tissue biopsy was found in 1955, further sections confirmed the diagnosis of anaplastic carcinoma, and so even the most sceptical were finally convinced.

Case 2: A local cure by pre-operative supervoltage irradiation and pneumonectomy. A farmer aged 56 had increasing cough and dyspnea and 35 lb. weight loss over a six-month period, and pain in the back and blood-streaked sputum for one month. In the chest x-ray film (Fig. 3) the right thorax was opaque and the trachea shifted to the right; on bronchoscopy there was a tumor in the right main bronchus at the level of the main carina, and the biopsy was reported as epidermoid carcinoma. A tumor dose of 6250 r was given in one month with 1000 kv x-rays through opposed 10 x 10 cm anterior and posterior fields centered on the right main bronchus; the tumor regressed so that the upper lobe aerated (Fig. 4), then a plug of tumor an inch in size was coughed up (Fig. 5), followed by aeration of the middle and lower lobes (Fig. 6) and complete relief of the symptoms of cough, dyspnea and cachexia. At subsequent follow-up visits the patient remained symptom-free, but five months after treatment bronchoscopic biopsies showed persistent cancer in the bronchus intermedius and the main carina tumor-free. A right radical pneumonectomy was therefore performed; the 7 cm. tumor in the root of the right lower lobe had invaded the inferior pulmonary vein and adjacent pericardium, so this vein had to be transected at its junction with the left auricle, but all the hilar and mediastinal nodes were free from metastatic carcinoma. The patient remained well and working for two and one-half years, but then developed vertigo and staggering gait, clearly due to cerebellar metastasis. Since brain metastases are usually multiple, the whole brain was irradiated with 250 kv x-rays through opposed 11 x 20 cm. lateral fields to a tissue dose of 2950 r in five weeks, but without improvement in symptoms or signs. He died three months after this treatment, and at autopsy the only cancer found anywhere in the body was a solitary cerebellar metastasis of epidermoid carcinoma.

Case 3: Residual disease after simple pneumonectomy cured by postoperative supervoltage irradiation for 11 years. A woman aged 44 had a left simple pneumonectomy in 1942 for oat-cell carcinoma; the inferior pulmonary vein was both grossly and microscopically surrounded and invaded by the carcinoma, and was transected through tumor outside the pericardium. This region of known residual tumor was then given a tumor dose of 4200 r in 26 days with 1000 kv x-rays through opposed 8 x 8 cm. anterior and posterior fields. There have been neither symptoms nor signs of recurrent growth or metastases since, and in 1953—11 years after treatment—she reported that she was looking after her house and garden as usual and was in excellent health.

Case 4: Excellent palliation resulting from failed curative radiation therapy. In October 1956 a man aged 53 began to have generalized 'rheumatic' pains with inter-

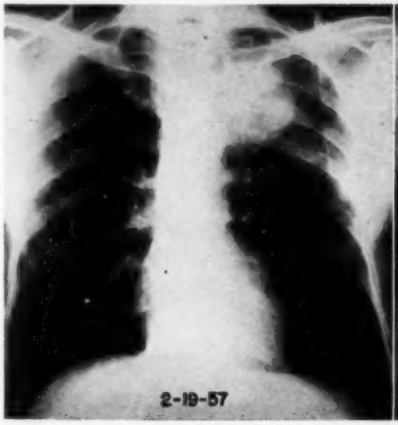

FIGURE 7

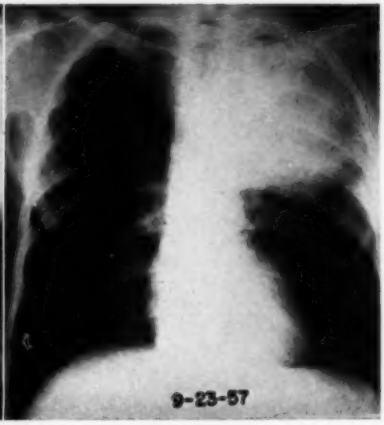

FIGURE 8

FIGURE 7 (Case 4): Feb. 19, 1957—carcinoma of left upper lobe. FIGURE 8 (Case 4): Sept. 23, 1957—appearance of tumor at beginning of x-ray therapy.

mittent joint swellings; he felt increasing weakness and lost six pounds. When he noticed gross clubbing of his fingers and toes he went to a municipal chest clinic, where he was told that he had a small tumor of the lung. He came to consult me in February 1957 because some years previously I had treated his small daughter for recurrent malignant teratoma of the pelvis. His chest x-ray film (Fig. 7) showed a circumscribed shadow in the left upper lobe, and arrangements were made for bronchoscopy and admission to hospital for resection. He did not keep these arrangements or answer inquiries, but returned in September 1957 because of severe chest pain. The tumor (Fig. 8) was much larger than in February but still appeared operable; he again refused any procedures other than x-ray therapy; the sputum contained numerous cancer cells although the type could not be specified. A tumor dose of 6050 r was given in six weeks with 1000 kv x-rays; early in the course of treatment the severe chest pain and the painful polyarthritis were completely relieved, and the tumor regressed and in the chest x-ray film one year after treatment (Fig. 9) its shadow cannot be seen. In January 1958 he noticed increasing headache, nausea, vertigo and sub-occipital pain; he was admitted to hospital with the clinical diagnosis of multiple cerebellar metastases, (C.S.F. protein was 150 mg./100 cc.), and made complete recovery following irradiation of the whole brain with 250 kv x-rays, tumor dose 3120 r in three weeks. He continued in good health until July 1959—he even regained an excellent head of hair after the complete epilation caused by irradiation —when he had a return of the painful polyarthritis and clubbing of the fingers and toes. He had no cough and no cancer cells could be found in the sputum, but the chest x-ray film was suggestive of a hilar node metastasis just below the aortic knob. On this occasion telecobalt rotation therapy was used in order to avoid producing skin erythema in the previously irradiated area, and again there was early improvement in the osteoarthropathy. It is also interesting that on both occasions, during the treatment of the primary tumor and of the hilar metastasis 22 months later, as the polyarthritis subsided a generalized pruritus occurred, particularly over the shins, and persisted for some weeks. Figure 10 shows the chest x-ray film in February, 1960.

Primary bronchogenic cancer is of course the commonest thoracic neoplasm, but the principles of radiation therapy which have been illustrated in this paper are equally valid for other types of malignant disease, and the results are generally somewhat better. Examples were shown of a mediastinal lymphosarcoma well for 10 years; Hodgkin's disease of the mediastinal and cervical nodes well for seven years; Ewing's tumor of the rib and pleural cavity without local recurrence for six years and then fatal metastases in the opposite lung; a large neuroblastoma of the posterior mediastinum successfully removed after preoperative radiation of the mediastinum; and various types of pulmonary metastases (liposarcoma, reticulum-cell sarcoma, osteogenic sarcoma, malignant synovioma, malignant teratoma, neuroblastoma, Wilms' tu-

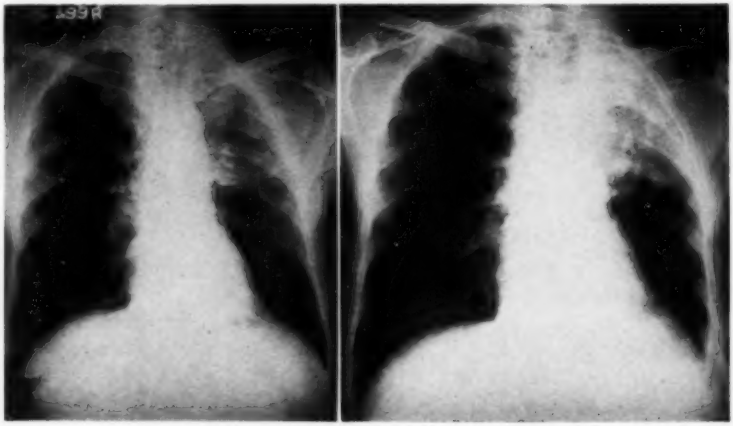

FIGURE 9 FIGURE 10

FIGURE 9 (Case 4): Sept. 23, 1958—no tumor shadow visible one years after 6050 r T.D. FIGURE 10 (Case 4): Feb. 2, 1960—patient symptom free.

mor) which disappeared following radiation therapy and did not recur for one or more years. Although in most cases the recurrence of hematogenous metastases is to be expected within a period of less than 12 months, the fact that there are even a few cases of prolonged control offers hope of improved treatment in the near future, since it is the radiation tolerance of the pulmonary alveoli which is the persent limiting factor. If some reliable means of preventing or treating radiation pneumonitis and pulmonary fibrosis could be found, it would be possible to give pulmonary metastases a more effective tumor dose; or if a truly synergistic chemotherapeutic agent were available, the present permissible tumor dose of, say, 2000 r would be more effective.

SUMMARY

From an evaluation of the present status of radiotherapy in thoracic neoplasms, both primary and metastatic, five suggestions are made for the improvement of present results:

1. Better appreciation by the medical profession of what can even now be accomplished.
2. Provision of more supervoltage x-ray and telecobalt apparatus, and of more trained radiation therapists to use them.
3. More use of intelligent pre-operative and post-operative irradiation, and of radioactive implants at operation.
4. More hopeful treatment of hematogenous metastases,
   (a) of primary bronchogenic cancer to the brain or liver.
   (b) of pulmonary metastases from extrathoracic primary sites.
5. Investigations directed to the discovery of
   (a) a truly synergistic chemotherapeutic agent
   (b) the significance of free-floating cancer cells in the blood
   (c) a means of preventing or treating radiation damage to the lungs.

RESUMEN

Después de una valuación del estado actual de la radioterapia en las neoplasias torăcicas tanto primarias como metastásicas, se hacen sugestiones para mejorar los resultados:

1. Mejor estimación por parte de los médicos de lo que puede obtenerse.
2. Provisión de mas supervoltaje en los aparatos de rayos X y de Cobalto, y mas técnicos adiestrados para usarlos.
3. Mayor uso de la radiación pre y postoperatoria inteligentemente aplicada, así como de implantaciones de substancias radioactivas durante la operación.
4. Tratamiento mas útil de las metástasis hematógenas:
   (a) de cáncer bronquiogénico a cerebro o hígado.
   (b) de metástasis pulmonares de partida extratorácica.
5. Investigaciones dirigidas al descubrimiento de:
   (a) un agente terapéutico verdaderamente sinérgico.
   (b) la significación de las celdillas libros flotantes en la sangre.
   (c) un medio para prevenir o tratar el daño de la radiación sobre los pulmones.

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Pulmonary Artery Pressure Studies
Does Over-Distension of the Lung Cause Hypertension?*

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In the postoperative period, a patient having pulmonary resection faces the problem of pleural space obliteration. Among the mechanisms involved are (1) shifting of the diaphragm, mediastinum and chest wall; and (2) distension of the remaining lung. The effects of these on pulmonary ventilation are well documented. It is not clear how much these mechanisms affect pulmonary vascular resistance or other cardiopulmonary function, since there is always the additional factor of loss of vascular bed with the resection.

Other investigations have shown that loss of pulmonary vascular bed beyond certain limits produces pulmonary hypertension.[1] Some healthy animals have survived staged massive pulmonary resections with as little as 15 per cent of their total pulmonary parenchyma remaining; however, such animals were then hypertensive and were not long term survivors. It was not clear whether distension of the remaining pulmonary parenchyma had a deleterious effect on this pulmonary hypertension.

Certain clinical situations raised a similar question. Lester and coworkers,[2] found that pulmonary hypertension may be anticipated later in life in children facing large pulmonary resections with subsequent over-distension. In adults, the problem is complicated by pulmonary parenchymal deterioration.[3] Pulmonary resection and subsequent over-distension may aggravate the effects of loss of vascular bed. However, cardiac catheterization on three patients who were five-year survivors of massive pulmonary resection suggested that simple over-distension of the lung is not a factor in elevating pulmonary artery pressures.[4]

An experiment was designed to determine whether the physiologic effects of massive resection of pulmonary parenchyma would be adversely affected by over-distension of the remaining lung.

Method

Fifteen mongrel dogs were used for the experiment. A typical animal received 15 mg. of morphine and 0.4 mg. of atropine as premedication. General basal anesthesia was maintained with intravenous 2.5 per cent Surital. A number six cardiac catheter was passed to the pulmonary artery via the right jugular vein. The femoral artery was cannulated. A cuffed endotracheal tube connected the animal with a standard closed circle absorption anesthesia machine for ventilation with 100 per cent oxygen. Endotracheal pressures were then measured through a catheter

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placed in the wall of the endotracheal tube. Catheters connected by Y tubes were placed in each intrapleural space. A separate intrapleural tube was used to add or subtract air from the thorax after chest closure.

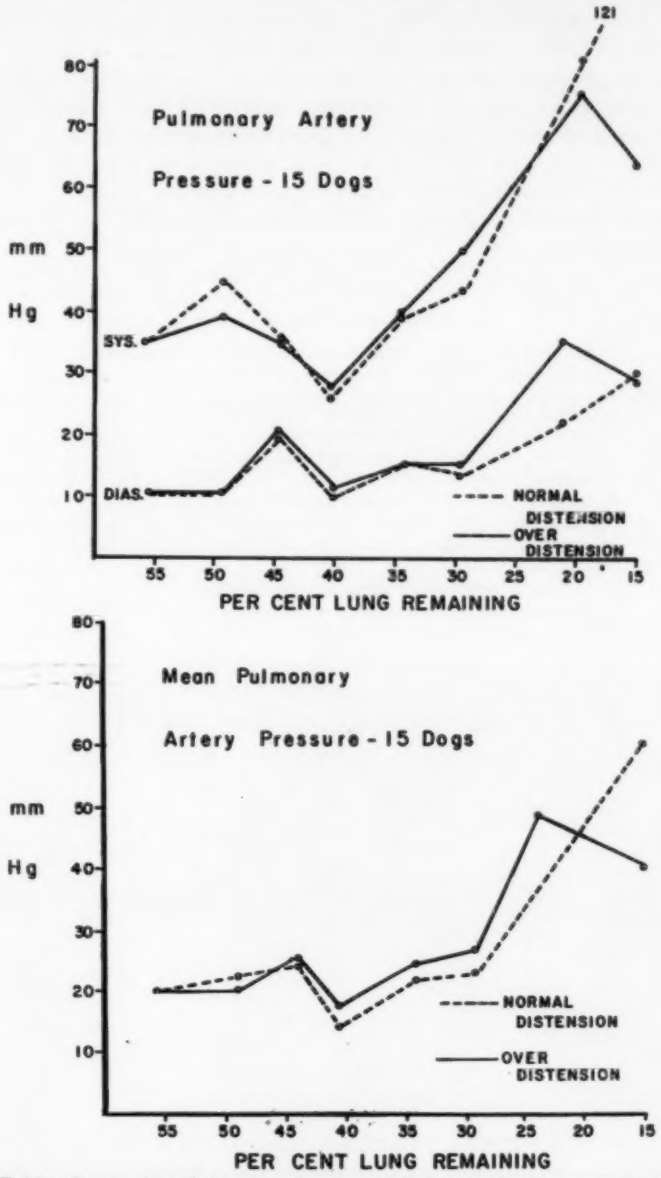

FIGURE 1A: Comparison between pulmonary artery pressures in normal distension and over-distension. Each point on the graph represents the averaged data from two animal experiments. Lung distension was accomplished by the removal of air from the pleural space. Pleural pressures at over-distension were —4 to —25 mm. Hg.

FIGURE 1B: Mean pulmonary artery pressures derived from Fig. 1A.

Statham gauges and a Grass Multichannel Recorder were used to monitor EKG, femoral and pulmonary artery pressures, endotracheal and intrapleural pressures. Then by bilateral transternal thoracotomy, 50 to 85 per cent of the total lung capacity was resected and the chest was closed. The animal's respiration was allowed to become spontaneous with endotracheal pressures hovering near zero.

Negative pressure inflation of the residual lung was accomplished by the removal of pleural air. Maximum distension of the remaining lung was assumed to occur when pleural air was completely evacuated. This steady state was then recorded by chest roentgenogram. "Normal" distension of the remaining lung was assumed to occur when pleural pressures were adjusted to normal values (0 to −10 mm Hg.) and confirmed by chest roentgenogram. The latter point was arbitrarily chosen to facilitate comparisons among the animals studied. (See Protocol)

PROTOCOL DOG No. 10

Procedure:	Left pneumonectomy, right upper and middle lobectomy	
9:30 A.M.	Preop. medication M.S. 15 mg. Atropine 0.4 mg.	
9:50 A.M.	P.A. catheterized under local anesthesia Rt. Femoral artery cannulated EKG monitored by oscillograph	
10:00 A.M.	Intravenous Surital 2½ per cent — 2.0 cc. I.V.	
10:03 A.M.	Femoral Artery Pressure 165/100	PAP 28/10
10:05 A.M.	Animal awakening 0.5 cc Surital I.V.	PAP 40/15
10:10 A.M.	Endotracheal tube, 100 per cent oxygen	PAP 24/12
10:11 A.M.	Thoracotomy begun — Respiration assisted	
10:17 A.M.	Chest Open	PAP 30/13
10:30 A.M.	Resection Completed — RL and ACC Lobes remaining (34 per cent)	PAP 37/16
10:53 A.M.	Chest Closed Pleural Pressure 0 to −5	PAP 37/12

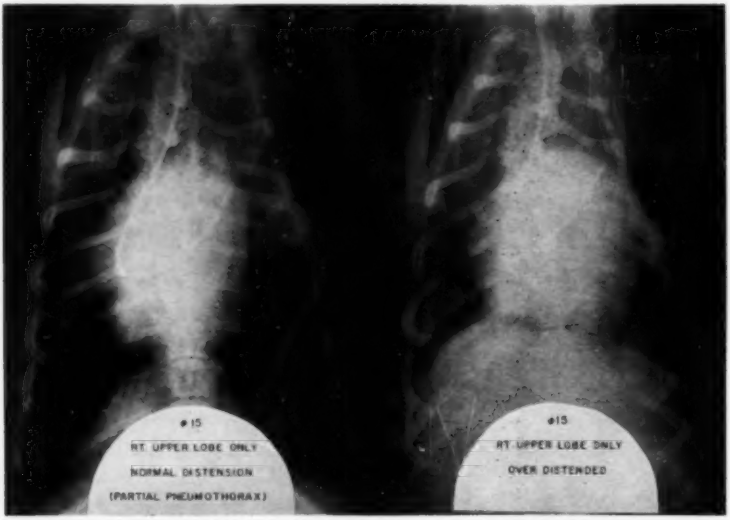

FIGURE 2A FIGURE 2B

FIGURE 2A: "Normal" distension following an 85 per cent pulmonary resection (right upper lobe remaining) See Fig. 3A. FIGURE 2B: Over-distension in the same animal.

11:05 A.M.	Spontaneous Respiration, Pneumothorax evacuated. Pleural Press. −3 to −18	PAP 32/10
11:50 A.M.	500 cc. air injected into pleural space Pleural pressure +4 to −12	PAP 44/18
12:03 P.M.	300 cc. air removed Pl. Press. 0 to +10	PAP 40/14
12:07 P.M.	200 cc. air removed Pl. Press. −3 to −20	PAP 35/13
12:10 P.M.	400 cc. air added to pleural space Pl. Press. +4 to −8	PAP 42/15
12:15 P.M.	440 cc. air evacuated from pleural space. Pleural Press. −2 to −26	PAP 32/10
12:30 P.M.	Procedure terminated	

Results

All animals exhibited some degree of pulmonary hypertension with massive resection of pulmonary vascular bed. Removal of as much as 50 per cent of the total lung capacity resulted in very little alteration of the systemic arterial pressures, however, the pulmonic arterial pressures in general were slightly increased. When the ablation of lung tissue was increased from 50 to as much as 85 per cent the pulmonary arterial pressures were further increased to as much as 100 to 300 per cent of the normal values.

This pulmonary hypertension was affected by the degree of distension of the remaining lung. Comparisons of pulmonic arterial pressures were

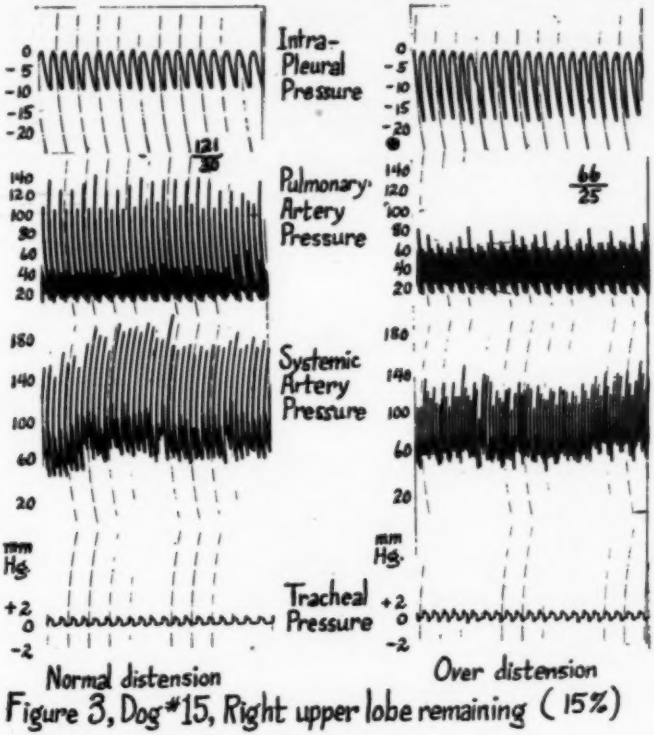

FIGURE 3A: Data recorded from the animal shown in Fig. 2A in "normal distension.
FIGURE: 3B: Data recorded from the same animal shown in Fig. 2B in over-distension accomplished by aspirating pleural air from the closed chest.

made when the remaining lung was at "normal" distension and at maximal distension. In the over-distended state pulmonic systolic pressures were in general slightly lower and diastolic pressures slightly higher than in the "normal" distension state. (Fig. 1A). The mean pressures however were not significantly different in the two states of distension until resections larger than 70 per cent were compared (Fig. 1B). With these larger resections over-distension of the remaining lung materially reduced pulmonic pressure and often lowered pulse rate. Marked shifts of the thoracic perimeter were noted on chest roentgenograms when over-distension and "normal" distension of remaining lung was compared (Figs. 2A and B).

Discussion

The effect of distension of the lung, produced in various ways, has been studied many times. Differences in interpretation of data have been confusing. Burton[5] has ably analyzed these confusions and has resolved them with his concept of transmural pressure which is defined as the difference between tissue pressure outside of the vessel and the intravascular pressure of the blood inside the vessel. He says:

(1) "In positive-pressure inflation, the transmural pressure of pulmonary vessels must decrease as the distending pressure is increased. (this would increase the resistance)."

(2) "In negative-pressure inflation (as in normal respiration) the transmural pressure must increase as the distension increases (this would decrease the resistance)."

(3) "When the perfusion pressure shares in the decrease in intrathoracic pressure in negative pressure inflation, as in Visscher's experiments, the transmural pressure decreases as the distension increases and resistance would increase."

The human postpneumonectomy state seems to be duplicated by the present animal experiment. Both are interpreted as examples of Burton's second statement above where the lung is distended by negative pressure inflation (pleural air aspiration) and the perfusion pressure (right ventricle) does not share in the negative pressure induced. For example, it will be noted in Figs. 3 and 4 that the changes in pleural negativity from "normal" to over-distension (7 to −10 Hg. change) resulted in far greater pulmonary artery pressure changes (20 to 50 mm.Hg. change). This would suggest that the right ventricular pressure does not share equally in all of the changes in intrapleural pressure. Admittedly the right ventricle could share a small part of pleural pressure changes. Exact mathematic definition of this partition is elusive but in this experiment the right ventricle would seem to share less than one fifth of the pleural pressure change. Alterations of pleural pressure, in the largest pulmonary resection

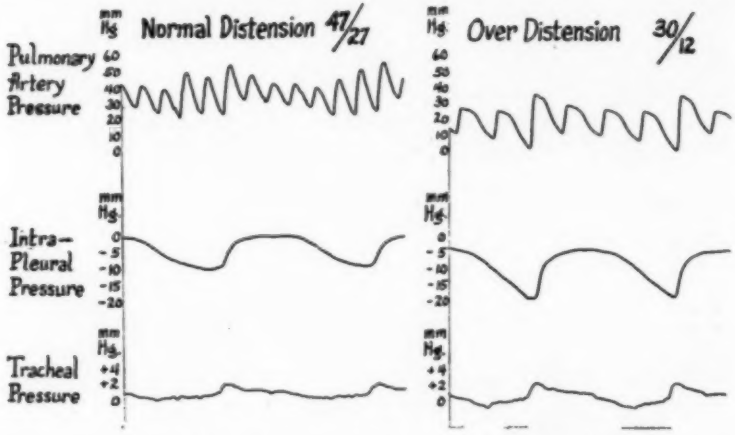

FIGURE 4: Data recorded following resection of 21 per cent of pulmonary parenchyma (left lower lobe remaining). Note lowering of pulmonary artery pressures with over-distension and slowing of pulse.

particularly, seem to affect pulmonary artery pressure mainly by changing diameter of all pulmonary parenchymal components including vascular bed.

Modest over-distension of remaining lung after pneumonectomy would appear to have a beneficial effect on the lesser circulation, assuming that the remaining lung is normal. Thus collapse procedures to prevent over-distension of remaining normal lung would appear unwarranted. The effect of resection and over-distension upon diseased lung tissue in animals and adult humans is under study.

SUMMARY

Fifteen mongrel dogs were subjected to resections of 50 to 85 per cent of total pulmonary tissue. In the closed postoperative chest, pulmonary artery pressure was measured with the remaining lung in "normal" distension and over-distension.

The results obtained demonstrated that over-distension of residual normal lung does not aggravate any pulmonary hypertension produced by large pulmonary resections.

From the standpoint of pulmonary hypertension this experiment would indicate that collapse procedures to prevent over-distension of normal lung are unwarranted.

RESUMEN

Se sujetaron 15 perros de raza híbrida a resecciones de 50 a 85 por ciento del total del tejido pulmonar. En el tórax cerrado después de la operación se midieron las presiones de la arteria pulmonar con el pulmón restante en distensión "normal" y sobredistensión.

Los resultados obtenidos demostraron que la sobredistensión del pulmón normal residual no agrava ninguna hipertensión pulmonar producida por grandes resecciones pulmonares.

Desde el punto de vista de la hipertensión pulmonar, este experimento indicaría que los procedimientos de colapso para evitar la sobredistensión, no están justificados.

RESUMÉ

Quinze chiens furent soumis à des résections portant sur 50 à 85% du tissu pulmonaire total. Dans le thorax fermé après l'intervention, la pression de l'artère pulmonaire fut mesurée avec le reste du poumon en distension "normale" et en hyperdistension.

Les résultats obtenus montrèrent que cette hyper-distension du poumon résiduel normal n'aggrave aucùnement l'hypertension de l'artère pulmonaire provoquée par des résections pulmonaires étendues.

Du point de vue de l'hypertension de l'artère pulmonaire, cette expérience semble indiquer que des procédés de collapsus mis en oeuvre pour empêcher l'hyper-distension du poumon normal sont sans objet.

ZUSAMMENFASSUNG

Fünfzehn Bastardhunde wurden Lungenresektionen von 50 — 85% des gesamten Organes unterzogen. In der nach der Operation verschlossenen Thoraxhöhle wurde der pulmonale Arteriendruck gemessen sowohl bei normaler Stellung der verbleibenden Lungenteile, als bei Überdehnung.

Die gewonnenen Ergebnisse zeigten, daß eine Überdehnung der verbliebenen normalen Lunge nicht imstande ist, rigendeinen pulmonalen Hochdruck zu verschlechtern, der durch ausgedehnte Lungenresektionen zu tande gekommen ist.

Vom Standpunkt des pulmonalen Hochdruckes gesehen zeigt diese Untersuchung, daß Kollapsmaßnahmen zur Verhütung einer Überdehnung der normalen Lunge unberechtigt sind.

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Serum Enzymes in Bronchogenic Carcinoma and Other Pulmonary Diseases*

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In recent years, medical investigators have reported the elevation of serum enzymes, particularly glutamic oxaloacetic transaminase (SGO-T)[1-4] and lactic dehydrogenase (LDH) in patients with neoplastic disease.[4-9]

Animal experiments have also indicated that: a) the lactic dehydrogenase activity of tissues containing transplanted tumor was higher than the corresponding non-tumorous tissue;[10] b) this activity generally follows tumor age;[11] and c) it also decreases with tumor regression.

In one clinical survey, 92 per cent of histologically proved carcinoma patients exhibited serum LDH activity above the normal range.[7] In another series, approximately one half of 173 patients with a variety of tumors were noted to have increased serum levels of SGO-T and LDH.[4]

Material and Methods

A study was undertaken to determine the diagnostic value of serum enzymes, particularly lactic dehydrogenase (LDH) in solitary pulmonary nodules and intrinsic lung mass densities. Serum levels were also recorded in patients who had received surgical or x-ray therapy for bronchogenic carcinoma in the hope of noting the response to treatment or to detect as early as possible tumor recurrence or spread.

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*The opinions or assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department of the Naval service at large.

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FIGURE 1: PA and lateral chest films revealing a right lower lobe epidermoid carcinoma.

TABLE 1 — SERUM LACTIC DEHYDROGENASE

Bronchogenic Carcinoma	34 cases
Normal range	6 cases
Above normal range	28 cases
(Initial and serial determinations)	

In most instances, tests were made at weekly or bimonthly intervals. The lactic dehydrogenase activity was determined by the method of Wroblewski and LaDue,[8] with slight modification.

Serum LDH activity of 52 normal adult subjects ranged between 105 and 300 units per millilitre. This group compares favorably with the 165 to 332 units per ml. in the controls obtained by MacDonald et al.[11]

Results

Table 1 indicates that the serum lactic dehydrogenase activity was found to be above the normal range in 28 or 82 per cent of 34 patients with histologically proved malignant lung tumors.

Lactic dehydrogenase activity returned to normal levels in all resected cases, and in the majority of patients who received x-ray therapy.

There were seven cases of solitary pulmonary nodules diagnosed following surgical resection. These included four non-specific granulomas, two histoplasmomas, and one oat cell carcinoma. The single elevated serum LDH occurred in the patient with the oat cell lesion.

Serum lactic dehydrogenase was elevated in 25 (71 per cent) of 35 patients with acute viral or bacterial pneumonia, Table 2.

Weekly LDH determinations demonstrated a return to normal in all these patients as the pneumonic process cleared clinically and radiographically.

Tables 3 and 4 reveal that tuberculosis and the majority of other pulmonary diseases (except pulmonary infarction and metastatic lung cancer) did not affect the blood levels of lactic dehydrogenase.

Table 5 summarizes the results of the serum glutamic oxaloacetic transaminase (SGO-T) and the serum glutamic pyruvic transaminase

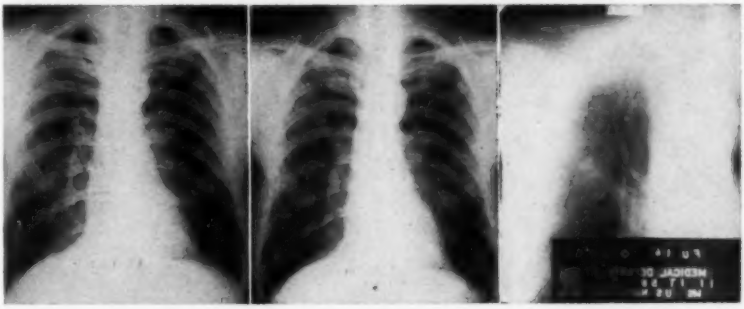

FIGURE 2a FIGURE 2b FIGURE 2c

FIGURE 2a: Parenchymal infiltrate in the second right anterior interspace. (May 19, 1958). FIGURE 2b: Slight increase in size of right upper lobe lesion. (October 23, 1958). FIGURE 2c: Tomographic section noting the nodular character of the right upper lobe lesion.

TABLE 2 — SERUM LACTIC DEHYDROGENASE

Pneumonia—Viral or Bacterial	35 cases
Normal range	10
Above normal range	25

TABLE 3 — SERUM LACTIC DEHYDROGENASE

	Normal	Elevated
Metastatic Ca to lung	4	4
Pulmonary Infarction	0	6
Sarcoidosis	5	1
Bronchitis acute	8	1
Asthma	7	1

(SGP-T) in the 34 cases of bronchogenic carcinoma. Twenty-six (76 per cent) of the patients had normal SGO-T and SGP-T values. There were seven with SGO-T elevations and four cases with increased SGP-T values.

In each instance of elevated serum transaminase, metastatic hepatic disease was obvious by clinical evaluation.

The serum transaminase was normal in 31 (86 per cent) of 36 patients with acute viral or bacterial pneumonia, Table 6. It is of interest to note associated pericarditis in three cases presenting with elevated serum glutamic oxaloacetic transaminase.

Case Presentations

The following cases will demonstrate our experience with lactic dehydrogenase activity.

Case 1: The posteroantero and lateral chest films of this 62 year-old man revealed a rounded mass density in the right lower lobe, (Fig. 1). This proved to be a non-resectable epidermoid carcinoma. The serum LDH was 822.

Case 2: A 42 year-old woman was treated by pneumonectomy for right upper lobe adenocarcinoma. Pre-operative serum LDH was 610. Following surgery, the lactic dehydrogenase activity returned to normal and then gradually climbed to 890 in six months.

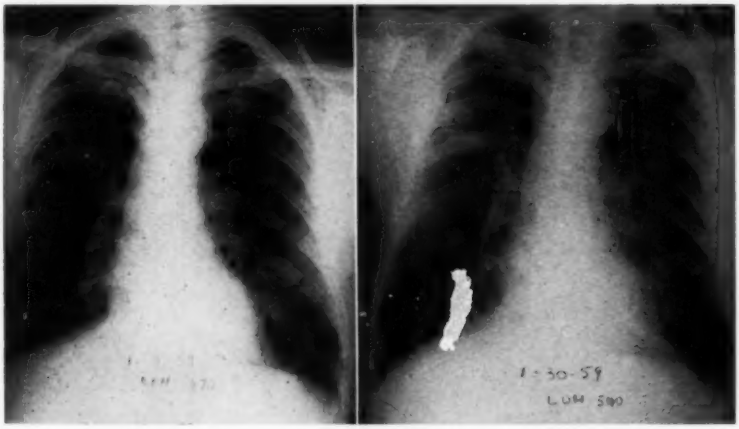

FIGURE 3a FIGURE 3b

FIGURE 3a: Further progression of right upper lobe process. (January 8, 1959).
FIGURE 3b: Thin-walled cavity in the right upper lobe. (January 30, 1959).

TABLE 4 — SERUM LACTIC DEHYDROGENASE

	Normal	Elevated
TB, Active	8	0
TB, Inactive	11	0
Granuloma, NS	4	0
Histoplasmoma	2	0
Histoplasmosis, Acute	2	0
Bronchiectasis	5	0
Emphysema	6	0

Despite additional surgical resection of a single cerebral lesion and x-ray therapy she subsequently expired.

Case 3: The patient presented with a rounded mass occupying the entire lower lobe of the left lung. The serum LDH of 2000 aided in the pre-operative diagnosis of bronchogenic carcinoma. Post-operatively the serum LDH fell to 200.

Case 4: Figures 2 and 3 demonstrate the diagnostic value of serial lactic dehydrogenase determinations. Figure 2a reveals a small parenchymal infiltrate in the second right anterior interspace on a posteroantero chest film dated May 19, 1958. Figure 2b is a followup chest x-ray dated October 23, 1959. A slight increase in the size of the right upper lobe lesion is noted. The serum lactic dehydrogenase was 170. Figure 2c represents a tomographic section noting the nodular character of the chest lesion. Figure 3a reveals further progression of the right upper lobe process and increase in serum LDH to 370. Figure 3b illustrates the pre-operative chest x-ray film with a thin walled cavity in the right upper lobe. The patient's serum LDH was 540. At surgery a resectable bronchogenic carcinoma was found. Post-operative serum LDH levels have ranged between 250 and 270.

Case 5: This 52 year-old man with non resectable epidermoid carcinoma of the left lower lobe had initial serum LDH of 766. Six weeks after x-ray therapy the serum lactic dehydrogenase fell to 300. SGO-T, SGP-T, BSP, and alkaline phosphatase remain within normal limits.

Case 6: This man had anaplastic bronchogenic carcinoma with diffuse metastasis. His serum LDH was initially 1,590 and subsequently rose to 3,275.

Case 7: A 49 year-old negro was admitted to the hospital when a routine chest x-ray film revealed a left hilar mass, pleural metastasis, and left pleural effusion. The pleural fluid was positive for malignant cells, but the serum LDH was within the normal range. After x-ray therapy, there was complete resolution of the left lung pathology from the x-ray film observation. However, there was a recurrence of the left hilar lesion in several months and obvious diffuse metastasis. The serum LDH gradually increased to a level of 4,750.

Case 8: A 37 year-old man was treated for extensive bilateral chickenpox pneumonia. Initial serum LDH was 1,575. Electrocardiograms and liver profile were negative. The serum LDH returned to normal as the patient recovered.

FIGURE 4a FIGURE 4b FIGURE 4c

FIGURE 4a: PA chest film noting mass density in the left upper lobe. FIGURE 4b: Follow-up chest film reveals slight resolution of the left upper lobe process. FIGURE 4c: Pre-discharge chest x-ray film with complete resolution of left upper lobe pneumonia.

TABLE 5 — SERUM TRANSAMINASE

Bronchogenic Carcinoma	34 cases
Normal SGOT and SGPT	26
Elevated SGOT	7
Elevated SGPT	4

TABLE 6 — SERUM TRANSAMINASE

Pneumonia—Viral or Bacterial	36 cases
Normal SGOT and SGPT	31
Elevated SGOT	5
Elevated SGPT	3

Case 9: Figure 4a reveals a mass density that was present in the left upper lobe of this 45 year-old white man. He was toxemic and sputum cultured diplococcus pneumonia. His serum LDH was 500. Following penicillin therapy, there was complete resolution of the left upper lung field process as demonstrated by followup chest x-ray films. (Figures 4b and 4c). The serum LDH gradually returned to 280. Complete diagnostic pulmonary evaluation was negative.

DISCUSSION

Serum lactic dehydrogenase activity is often increased in neoplastic disease. The highest levels have been observed in massive lung tumors and in bronchogenic carcinoma with widespread metastasis.

Elevated serum LDH values have also been noted in anemia, hepatic, and renal disease, infectious mononucleosis, myocardial infarction, congestive heart failure,[13] and in the present study, pneumonia, and pulmonary infarction.

The diagnostic significance of a single determination in cancer and leukemia detection is thereby limited.[14] However, the serial determination of serum lactic dehydrogenase activity in a suspicious case of pulmonary neoplasia may be an additional aid in the establishment of such a diagnosis. The differential diagnosis between pneumonia and lung tumor may also be clarified.

SUMMARY

1. Serial serum lactic dehydrogenase (LDH) determinations revealed increased activity in 82 per cent of patients with histologically proved bronchogenic carcinoma.

2. Serum lactic dehydrogenase activity was elevated in 71 per cent of patients with acute pneumonia, but interval studies noted a return to normal levels in all cases as the pneumonic process subsided.

3. Tuberculosis did not affect the blood levels of lactic dehydrogenase.

4. The serum lactic dehydrogenase frequently returned to normal following surgery, x-ray, or chemotherapy for bronchogenic carcinoma. Post therapy serum LDH studies appeared to be of prognostic value.

5. The serum transaminase was found to be of no particular value in the diagnosis of bronchogenic carcinoma.

RESUMEN

1. La dehidrogenasa láctica en el suero en serie (LDH) revela un aumento de la actividad en 82 por ciento de los enfermos con carcinoma bronquiogénico histológicamente comprobado.

2. La actividad de la dehidrogenasa láctica en el suero fué elevado en 71 por ciento de los enfermos con neumonía aguda, pero los estudios prolongados demostraron el regreso a lo normal en todos los casos en que el proceso neumónico cedió.

3. La tuberculosis no afectó los niveles sanguíneos de la dehidrogenase láctica.

4. La dehidrogenasa láctica en el suero frecuentemente vuelve a lo normal después de la cirugía, roentgenterapia o quimioterapia por carcinoma bronquiogénico. Los estudios de la LDH después de las operaciones parecen ser de valor pronóstico.

5. La transaminosa en el suero se encontró que no fué de valor especial en el diagnóstico del carcinoma bronquiogénico.

RESUMÉ

1. Des dosages en série de la déshydrogénase lactique du sérum révélèrent son augmentation chez 83% des malades atteints de cancer bronchique histologiquement mis en évidence.

2. L'activité de la déshydrogénase lactique du sérum se montra élevée chez 71% des malades atteints de pneumonie aiguë, mais des observations espacées montrèrent un retour à des taux normaux dans tous les cas malgré la persistance de l'affection.

3. La tuberculose n'affecta pas les taux sanguins de la déshydrogénase lactique.

4. La déshydrogénase lactique du sérum revint fréquemment à la normale après intervention, traitement radiothérapique ou chimiothérapique pour cancer bronchique. Des observations sur le taux de la déshydrogénase lactique du séruum après traitement ont paru avoir une valuer pronostique.

5. Les auteurs ont constaté que la transaminase du sérum n'a pas de valeur spésifique pour le diagnostic de cancer bronchique.

ZUSAMMENFASSUNG

1. Reihenmässige Bestimmungen der Serummilchsäure-Dehydrogenase (LDH) ergaben eine erhöhte Aktivität bei 82% der Patienten mit histologisch gesichertem Bronchialcarzinom.

2. Die Aktivität der Serummilchsäure-Dehydrogenase war ebenfalls erhöht bei 71% von Kranken mit akuter Pneumonie; aber zwischenzeitliche Untersuchungen ließen eine Hückkehr zu normalen Werten in allen Fällen erkennen, bei denen der pneumonische Prozess abflaute.

3. Eine Tuberkulose hatte keinen einfluß auf die Blutspiegelwerte der Milchsäure-Dehydrogenase.

4. Die Serummilchsäure-Dehydrogenase bildete sich häufig bis zu normalen Werten zurück im Anschluß an operative Eingriffe, Strahlen- oder Chemotherapie bein Bronchuscarzinom. Untersuchungen der Serum LDH nach Behandlung scheinen prognostische Schlüsse zu erlauben.

5. Für die Serumtransaminase ergabsich, daß ihrer Bestimmung keine besondere Bedeutung zukommt bei der Diagnose des Bronchuscarzinoms.

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Pulmonary Atelectasis Complicating Bronchial Asthma*

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Bronchial obstruction should be treated immediately and vigorously. Bronchoscopic aspiration may be essential to secure adequate bronchial drainage and preserve pulmonary function. Waldbott[1,2] states all moribund asthmatics should be given the benefit of bronchoscopic aspiration. He reports bronchoscopy to have been life-saving in seven out of eight critically ill asthmatic patients. Post-mortem examinations[3] on persons dying in status asthmaticus have revealed the smaller bronchi to be occluded by thick impacted mucous.

Atelectasis of varying degree is often present in allergic asthma caused by mucoid obstruction of the smaller bronchi.[4] Areas of increased density are occasionally manifested on chest x-ray films during asthmatic attacks. These shadows are sometimes evanescent if the patient is able to cough out the thick mucoid casts which are occluding the smaller bronchi. If the occluding mucous is persistent, organization may take place and a permanent shadow remain on the chest film. This may have to be differentiated at a later date from the other pulmonary pathology, a difficult procedure, sometimes requiring resection before a definite diagnosis can be made.[5]

Often the presence of fever, hemoptysis, chest pain and a history of expectoration of mucous casts will suggest the possibility of segmental atelectasis. Bronchial stenosis was found to be present in 30 per cent of one series of asthmatic patients.[6] Though others report a lower incidence, its presence favors retention of secretions, obstruction of air passages, infection and destruction of pulmonary parenchyma.

Treatment by bronchoscopic aspiration, dilatation and lavage as well as the use of antibiotics may be of value in preventing early development or progression of this condition.

Status asthmaticus which does not respond to treatment including adrenal steroids or corticotrophins or which relapses while the patient is receiving adequate therapy should suggest the possibility of some complication such as pulmonary atelectasis, infection, heart failure or others. The diagnosis of atelectasis even of a large pulmonary segment is not always easy to make clinically and must often be made or confirmed by a chest x-ray film. Diminished breath sounds, decreased or absent vocal fremitus, change in the percussion note over an atelectatic area may be obscured by loud asthmatic wheezing. The presence of localized excessive wheezing about the atelectatic areas is said to be of diagnostic value in suggesting a collapsed pulmonary segment. Chest pain, fever and hemoptysis may also direct attention to this possibility.

The following case illustrates the sudden development of massive lobar atelectasis in an asthmatic patient who had previously responded well to treatment.

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FIGURE 1: Erect posterior anterior view of chest.

FIGURE 2: Lateral view of chest, showing atelectasis of lower lobe of left lung.

FIGURE 3: Lateral view of chest, showinging re-expansion of lower lobe of left lung.

Miss G.R., a white woman, age 56, was admitted to the hospital on March 13, 1958 in an asthmatic crisis. The asthmatic attack began six days before admission when she suffered a febrile upper respiratory tract infection. Fever had subsided in response to antibiotic therapy; however, at the time of hospitalization the asthma was resistant to amelioration by epinephrine and aminophyllin.

Past history revealed episodes of bronchial asthma since adolesence. Eight years before, she had been hospitalized with a diagnosis of bronchial asthma and bronchopneumonia, from which she made an uneventful recovery.

On admission, the patient was in respiratory distress. Respiration was labored and her cough was productive of a thick muco-purulent sputum. She was physically exhausted. Chest x-ray film at the time of admission was interpreted as showing slight thickening of the pleura over the right apex, slight thickening of the short fissure, the lung fields were clear. Blood pressure was 154/80; respiration, 28/min; temperature, 98.6 F. Complete blood count was: hemoglobin 16.2 grams; white blood cells, 14,700; neutrophiles, 80 per cent; lymphocytes, 17 per cent; monocytes, 3 per cent.

She responded favorably to oxygen and adrenal steroid therapy. Intermittent positive pressure treatment with administration of a mixture of Isuprel and Alevaire was also used. Antibiotics were continued.

Preparation for discharge was contemplated when she suddenly complained of a severe continuous pain in the left lower portion of her chest. The pain was exacerbated by deep inspiration and coughing, it radiated posteriorly. Cough which had formerly been productive now increased in frequency, but produced only a scant thin mucoid sputum. She was afebrile and there was no hemoptysis. Diminished breath sounds and vocal fremitus were noted posteriorly over the left lower chest. Chest x-ray films, Figures 1, 2, showed atelectasis of the left lower lobe. Intermittent positive pressure treatment which had been discontinued was resumed with no apparent benefit. The bronchoscopist aspirated copious amounts of muco-purulent sputum from the left mainstem bronchus and the left lower lobe bronchus. Auscultation at this time revealed the re-entrance of air into the lower lobe. Lavage and aspiration were performed.

Subsequent chest x-ray film, Figure 3, showed complete re-expansion of the collapsed lobe.

She has suffered several recurrences of bronchial asthma since discharge from the hospital. There has been no further complication and her response to treatment has been good.

Bronchoscopy is not without risk. The trauma of the procedure may further increase edema and irritation of the bronchial mucosa. Sensitivity reactions present the greatest hazard. They may be minimized by careful pre-bronchoscopic preparation. Anti-histamines may be used, many of these patients will be already receiving adrenal steriod therapy. Anesthesia should be as light as is compatable with adequate passage of the bronchoscope. Epinephrine may be given intravenously if necessary, at the direction of the bronchoscopist who has the mucosa directly in view.

SUMMARY

Bronchoscopic aspiration and lavage may be of great value in persons suffering from intractable bronchial asthma. Persistence of asthmatic paroxysms in spite of adequate therapy suggests the presence of some complication. Careful physical and roentgenographic examination will often reveal the presence of previously unsuspected atelectasis.

RESUMEN

La aspiración broncoscópica y el lavado pueden ser de gran valor en las personas que sufren de asma bronquial intratable.

La persistencia de los paroxismos asmáticos a pesar de un tratamiento apropiado, sugiere la presencia de alguna complicación.

Los exámenes físico y radiológico cuidadosos, revelarán a menudo la presencia de atelectasia antes no sospechada.

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Cholesterol Pneumonitis*

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In 1949, Waddell et al[1] reported 10 operative cases of a peculiar form of chronic interstitial pneumonia whose paramount microscopic feature consisted of collections of large foam cells (macrophages containing lipid) within the alveoli. These were unassociated with significant bronchial disease or pulmonary suppuration but were accompanied by parenchymal changes found in other types of chronic pneumonitis. The content of these alveolar macrophages was determined to be cholesterol and its esters, and the condition was termed "cholesterol pneumonitis." The foam cells in these cases were distinct from those fat-containing lipophages found in exogenous lipoid pneumonia, and no patient had used oil nasally or orally. In six of the 10 patients subjected to thoracotomy, the preoperative diagnosis was carcinoma of the lung.

In 1953, Fineberg[2] described six additional cases of the same entity, but since that time few additional reports[3,4] have been published.

From this review, we have excluded all cases of chronic non-specific pneumonitis not showing diffuse involvement of alveoli by foam cells, cases of exogenous lipoid pneumonia, and those of suppurative and neoplastic lesions of the lung, in many of which occasional focal collections of such foam cells may be found. Xanthomas[5] and "post-inflammatory tumors'"[6] have likewise been excluded as separate pathologic entities.

The following five patients presented symptomatic pulmonary lesions which were persistent or progressive and which were suspected of representing bronchogenic carcinoma. None had used oily medications in any form. All underwent pulmonary resection with recovery, and in each instance there was segmental or lobar consolidation comprised principally of alveolar collections of cholesterol-containing macrophages.

Case Reports

Case 1. S.P., a 42-year-old laborer was admitted to St. Mary's Hospital, Brooklyn, New York on October 27, 1954 because of cough and fever of seven weeks duration. During this time he had been treated for pneumonia of the upper lobe of the right lung with various antibiotics without satisfactory response. His cough had become productive of blood-tinged sputum, and some pain and discomfort had appeared in the right upper thorax and shoulder. There was no history of previous chest disorder and no known contact with tuberculosis; he had smoked one pack of cigarettes daily for 25 years.

Physical examination on admission was unremarkable except for diminished breath sounds and dullness to percussion over the right upper lung field. Roentgenograms of the chest showed consolidation of the apical and posterior segments of the right upper lobe. Bronchoscopic examination showed slight distortion but no obstruction of the right upper lobar bronchus. Sputum smears for acid-fast bacilli were negative.

On November 2, 1954, thoracotomy was performed with findings of firm consolidation of most of the upper lobe and many apical pleural adhesions. Hilar nodes were moderately enlarged and firm, and the surgeon felt he was dealing with carcinoma. Accordingly, right pneumonectomy was carried out, and the patient is now well.

Gross and microscopic examination of the lung revealed a hard contracted upper lobe showing diffuse alveolar exudation of lipophages as well as associated fibrosis, bronchiolar distortion, and arteriolar thickening. The hilar nodes showed only lymphadenitis.

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Case 2. J.D., a 59-year-old married librarian, was admitted to Nassau Hospital on September 14, 1957 complaining of right anterior chest pain of five weeks duration. This had been associated with fever up to 103°F. and a productive cough with thick sputum which was blood-streaked on one occasion. She had complained of some dyspnea especially in the supine position.

Physical examination revealed dullness to percussion and absent breath sounds over the middle lobe area. A hemogram showed the following: Hb. 10.5 grams; WBC 30,000, smear normal. Roentgenograms of the chest demonstrated consolidation of the middle lobe. Bronchoscopy revealed serous secretion emanating from the middle lobe orifice. Bronchial washings were negative for tumor cells and acid-fast bacilli.

On September 20, 1957, right thoracotomy revealed the consolidated middle lobe which was densely adherent to adjacent lung and parietal pleura. As the surgeon felt this was most probably a benign condition, middle lobectomy was performed, and her convalescence was uneventful.

Examination of the lobe showed numerous adhesions and consolidation of both segments due to cholesterol-containing macrophages within the alveoli.

Case 3. H.C., a 35-year-old welder had complained of frequent head colds and chronic non-productive cough for about one year. One month prior to hospitalization his cough had become productive of thick mucoid sputum, and two weeks previously he had had a frank hemoptysis of red blood. This latter had been repeated four or five times with production of small amounts of blood on each occasion. He had smoked one pack of cigarettes daily for 17 years.

Physical examination revealed a robust sthenic individual with no abnormal findings. Sputum smears and cultures were unrevealing. Roentgenograms of the chest showed a moderately dense infiltrate in the superior segment of the right lower lobe. Bronchoscopic examination showed no abnormality. The right superior segmental orifice was clearly patent.

On September 25, 1957, right thoracotomy was performed with the finding of consolidation of the superior segment of the lower lobe. There were no pleural adhesions or enlarged hilar nodes, and the remaining lung appeared normal. Lower lobectomy was carried out, and his recovery was uneventful.

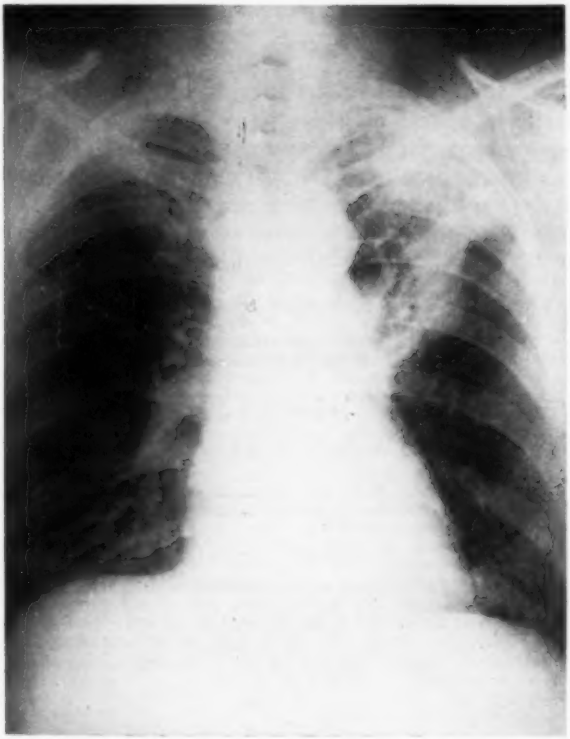

FIGURE 1: P-A Chest film (Case 5) showing lesion in left upper lobe.

Pathologic examination of the lobe showed a contracted and uniformly consolidated superior segment. There was no gross or microscopic bronchial abnormality. The alveolar walls were thickened, and the lumina contained collections of lipid-laden macrophages. Their cytoplasm appeared bright red with sudan stain.

Case 4. A.S., a 61-year-old clerical worker, consulted his physician because of fatigue, cough, and intermittent chills and fever of three weeks duration. For one week he had complained of pain in the right chest, and his cough had become productive of blood-streaked sputum. He had smoked one and one-half packs of cigarettes daily for the previous 38 years.

Physical examination on admission to the hospital revealed only a few coarse rales over the upper portion of the right lung field. Sputum smears for acid-fast bacilli were negative, and one sputum culture was subsequently negative for same after eight weeks.

Roentgenograms of the chest were interpreted as beginning atelectasis of the right upper lobe. Bronchoscopic examination demonstrated only a thick mucoid secretion in the right upper lobar orifice. He was discharged and later readmitted with persistent symptoms and roentgenographic findings.

Right thoracotomy was performed on February 13, 1958 revealing a contracted and consolidated upper lobe with a few pleural adhesions. A few enlarged soft nodes were present at the primary hilum. Right upper lobectomy was carried out, and his convalescence was uneventful.

Pathologic examination of the specimen showed almost complete consolidation due to alveolar foam cells and surrounding fibrosis.

Case 5. R.G., a 41-year-old painter was well until July, 1958, when he developed a febrile illness characterized as pneumonia by his physician. After antibiotic treatment at home his symptoms subsided, but recurred six weeks later. In September, 1958, he complained of cough, dull left chest and shoulder pain, chills, fever, and malaise. Following a frank hemoptysis he was admitted to another hospital for evaluation and treatment. Roentgenograms of the chest at that time showed a radially oriented smooth oval density in the left upper lobe. Findings at bronchoscopic examination were reported normal. Left prescalene fat pad excision revealed normal nodes. Following a course of antibiotic therapy, his symptoms subsided, and he left the hospital against advice. During the ensuing three months he was readmitted on two more occasions because of recurrence of symptoms, each time leaving against advice when antibiotics effected temporary relief. Successive roentgenograms of the chest showed progressive enlargement of the left upper lobe density.

He was finally admitted to Mercy Hospital, Rockville Center, N. Y. on February 10, 1959 for operation. His principal complaints at this time were severe chest pain and intractable productive cough with recurrent hemoptysis. Physical examination showed a chronically ill man with evidence of pallor and weight loss. There were diminished breath sounds with coarse rales over the upper lobe of the left lung and evidence of clubbing of the digits.

Sedimentation rate was 29 millimeters (one hour). Roentgenograms of the chest (Fig. 1) showed a homogenous infiltration of the upper lobe radiating from the hilum.

Left thoracotomy, performed on February 12, 1959, revealed a hard mass occupying the apicoposterior segment of the upper lobe. The overlying pleura was dimpled, and several large soft nodes were present at the primary hilum and in the superior mediastinum. Excision of one of the latter showed no evidence of tumor. The operative diagnosis was bronchogenic carcinoma, and resection of the upper lobe was performed in continuity with the hilar nodes.

Pathologic examination showed dense consolidation due to cholesterol-containing phagocytes and marked surrounding fibrosis.

Discussion

Each of the foregoing patients had had hemoptysis which varied from simple blood streaked sputum to frank recurrent production of red blood. None had history of previous pulmonary disease. All except one (Case 3) were past 40 years of age, and all were cigarette smokers.

Roentgenographic examination of the chest showed unilateral lesions in all cases and was strongly suggestive of malignancy in three of the five (Cases 1,4,5). Major bronchial obstruction could not be demonstrated in any case by direct and retrograde bronchoscopic examination. Noteworthy is the fact that even at operation in Cases 1 and 5 the surgeon felt he was dealing with bronchogenic carcinoma.

The etiology of this condition has not been clearly defined.[7] Bacterial studies of sputum and resected specimens have been non-specific. In 1954 Waddell[8] experimentally produced almost identical pathologic changes in rabbits by injecting their bronchi with Klebsiella Pneumoniae organisms and feeding them high cholesterol diets. The animals developed pulmonary consolidations characterized by foam cells desquamating from alveolar wall into lumen. These and other experiments point to an endogenous source of the cholesterol (from blood) with same traversing a damaged capil-

FIGURE 2

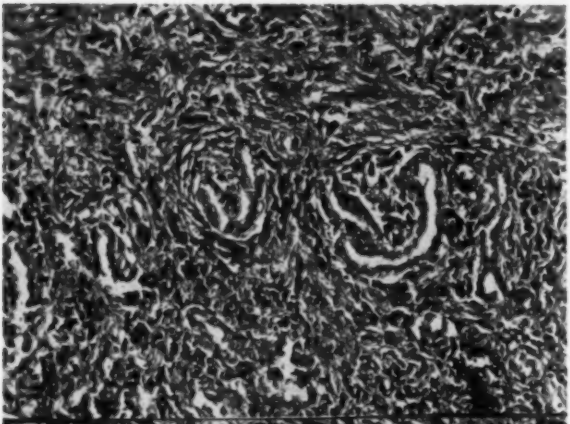

FIGURE 3

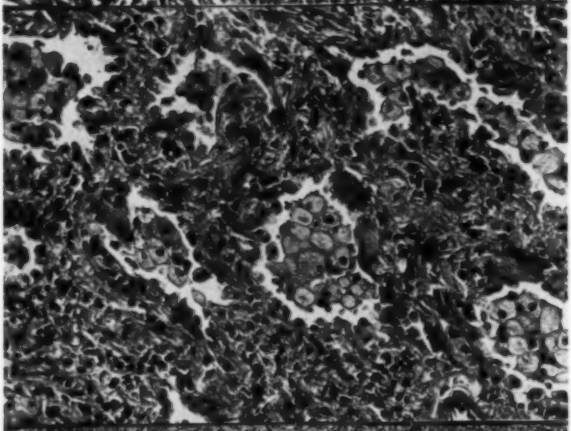

FIGURE 4

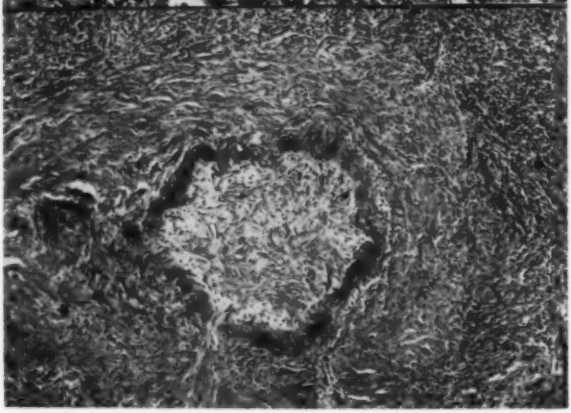

FIGURE 2: Photomicrograph (Case 5) demonstrating epithelialization of the alveoli.
FIGURE 3: Photomicrograph X200 (Case 4). Collections of foam cells demonstrating their morphology.
FIGURE 4: Photomicrograph X200 (Case 1) showing arteriole which has undergone occlusion and partial recanalization. Note its greatly thickened wall.

lary to enter the alveolar septal cell which desquamates into the lumen. It seems tenable, therefore, that in man cholesterol pneumonitis may be a reaction to alveolar and/or capillary injury of undetermined cause, possibly in the presence of hyperlipemia.

Pathologic Aspects

The gross and microscopic features of this entity possess characteristics which make the diagnosis possible. Since focal collections of these lipophages may be seen in specimens resected for bronchiectasis, lung abscess, tumor, and other diseases, these conditions must be excluded. This entails careful study of the gross specimen and histologic slides together with an evaluation of all the clinical and laboratory findings.

In the present cases all of the resected specimens revealed similar gross and microscopic changes, allowing for certain features which varied according to the stage of the disease. Pleural adhesions were noted in four of the specimens and were concentrated over the site of consolidation. The lung tissue was firm and rubbery in consistency with reduction in size. The cut section revealed a diffuse pneumonic process with segmental or lobar distribution. There was peculiar mottling and gray discoloration of the parenchyma with varying amounts of fibrosis. None of the usual features of a neoplastic process was present.

Microscopically there was considerable distortion of the normal architecture due to interlobular fibrosis, thickened and fibrosed alveolar walls, areas of atelectasis, concentration of lymphoid cells, epithelialization of some of the alveolar walls (Fig. 2), and conspicuous presence of numerous lipoid macrophages within the alveolar spaces (Fig. 3). Their nuclei were centrally placed and the cytoplasmic lipid formed individual droplets. These macrophages stained brilliantly with Sudan dyes and were also noted in the interstitial tissue. Occasional arteries showed marked intimal proliferation with narrowing or occlusion of the lumen, and in one instance, recanalization of the occluded lumen (Fig. 4). In some areas there was a prominent peribronchial infiltration with lymphocytes. These findings are occasionally present to varying degrees in other conditions, particularly in stenosis of a major bronchus from any cause. However, no specimen in this series showed any obstruction of the lobar, segmental, or subsegmental bronchi.

The lymph nodes were small to walnut-sized and soft. They showed only chronic lymphadenitis and reticular hyperplasia to varying degrees. Foam cells were conspicuously absent in all sections, suggesting that they do not metastasize.

Pathologic differentiation of this entity from other types of pneumonitis and granulomatous conditions should present little difficulty. Exogenous lipoid pneumonia differs microscopically in that the cell nucleus is eccentric and the red cytoplasmic lipid is confluent (signet ring cell) when sudan stain is used. The quite rare pulmonary xanthoma is a circumscribed tumefaction without alveolar spaces. Other types of chronic pneumonitis will show at best only occasional focal areas of foam cells, and some associated bronchial or specific parenchymal disease may be present.

SUMMARY

Cholesterol pneumonitis is an uncommon type of chronic progressive pulmonary consolidation which may resemble bronchogenic carcinoma both clinically and radiologically. Five cases of this condition have been presented; all underwent thoracotomy and resection because carcinoma could not be ruled out. The pathologic characteristics and possible etiology of this condition as well as its differentiation from similar entities such as lipoid pneumonia, are discussed.

RESUMEN

La neumonitis por colesterol es una forma poco común de consolidación pulmonar crónica progresiva que puede parecerse al carcinoma bronquiogénico tanto clínica como radiológicamente.

Se han presentado cinco casos de este padecimiento; todos se sujetaron a toracotomía y resección, porque no se pudo descartar el carcinoma. Se diserta sobre las características anatomopatológicas y la etiología posible de este padecimiento así como su diferenciación de afecciones semejantes, tales como la neumonía lipóidica.

RESUMÉ

La pneumonie à cholestérol est un type inhabituel de condition pulmonaire chronique et progressive, qui peut ressembler à un cancer bronchique tant cliniquement que radiologiquement. Cinq cas de cet état sont présentés: tous subirent une thoracotomie et une résection parce que le cancer n'avait pu être éliminé. Les auteurs discutent las caractéristiques anatomo-pathologiques, et l'origine possible de cet état, ainsi que sa différenciation avec des entités semblables telles que la pneumonie lipoïdique.

ZUSAMMENFASSUNG

Cholesterol-Pneumonie stellt eine ungewöhnliche Form einer chronischen und fortschreitenden pulmonalen Verdichtung dar, die einem Bronchuscarzinom ähnlich sehen kann, sowohl in klinischer wie auch in räntgenologischer Hinsicht. Es wurde über fünf Fälle dieser Erkrankung berichtet; sämtlich waren mit Thorakotomie und Resektion behandelt worden, weil ein Carzinom nicht auszuschliessen war. Diskussion der pathologisch-anatomischen Merkmale und der möglichen Ätiologie dieses Zustandsbildes ebenso wie ihre Differenzierung von ähnlichen Krankheitszuständen sowie z.B. der Lipoid-Pneumonie werden besprochen.

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Diffuse Pleural Mesothelioma

Report of a Case in an Adolescent

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Diffuse pleural mesotheliomas are comparatively rare tumors. Campbell[1] gives a rate of 0.11 per cent or about one case per 900 autopsies. In the early stages of the disease when treatment may be of value, the possibility of primary pleural tumor may not be considered. When the true nature of the condition becomes seriously suspected it is almost certainly too late to carry out any effective treatment. The present case is of interest also because of the youth of the patient.

Clinical Summary

This girl's illness started in October, 1957, when she was 16 years of age. She stated she had influenza at this time with quite a severe persistent cough. She was off school for a few days. Her cough improved quite quickly, but thereafter she tired easily. She lost weight, and for about a month before seeking medical attention in the middle of February, 1958, she suffered from left-sided pain of which she complained on admission to hospital on February 17, 1958. She also had pain in the back and in the neck. Her appetite was poor, she lacked energy and had a slight cough. On examination at this time, she appeared pale and tired, and the only clinical findings of note were dullness and absence of breath sounds over the lower half of the left lung. X-ray film of the chest showed an obscure left border of the heart and the left diaphragm was invisible. A large pleural effusion was seen involving the left hemithorax and extending as high as the anterior portion of the fourth rib. The visible portions of the lung fields were clear. Blood examination on admission showed a hemoglobin of 74 per cent (10.6 gm. per 100 ml.), and a hematocrit of 38 per cent. The white cell count was 6,350 with 80 per cent neutrophil polymorphs, 15 per cent lymphs, 1 per cent monocytes, 2 per cent eosinophils and 2 per cent band forms. The sedimentation rate was 77 mm. in one hour (Westergren). The first thoracentesis yielded 1100 cc. of blood-stained fluid, and x-ray film then showed moderate pleural thickening along the left lower margin of the chest with some infiltration of the left lower lobe. Two further thoracenteses were done prior to her discharge from hospital on March 7, 1958, and on the last occasion only 15 ml. of blood-stained fluid was obtained. X-ray film on March 6, 1958, showed the left diaphragm elevated and the left costophrenic angle quite dull. There was still some fluid confined largely to the anterior part of the left hemithorax, but the upper portion of the left lung field and the right lung remained clear. There was still some infiltration at the left base. During hospitalization she complained at times of severe back pain, but on discharge she was ambulant with no complaint. Her treatment on this admission was symptomatic. Examination of the pleural fluid on each occasion was negative for tumor cells.

FIGURE 1

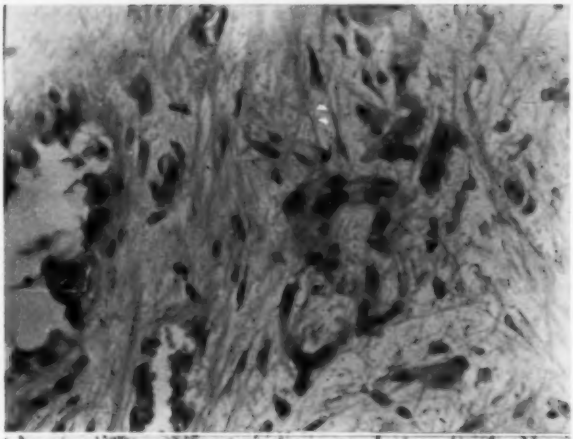

FIGURE 2

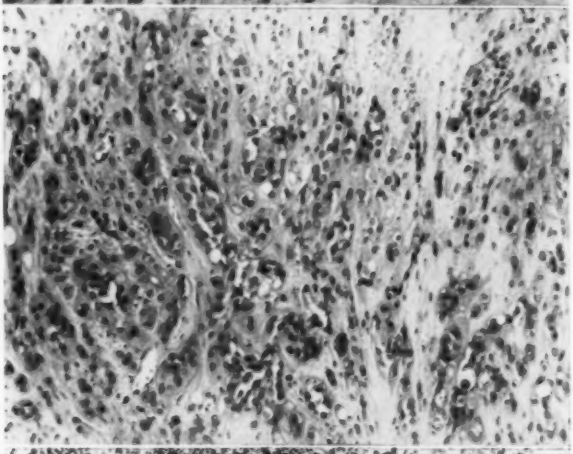

FIGURE 3

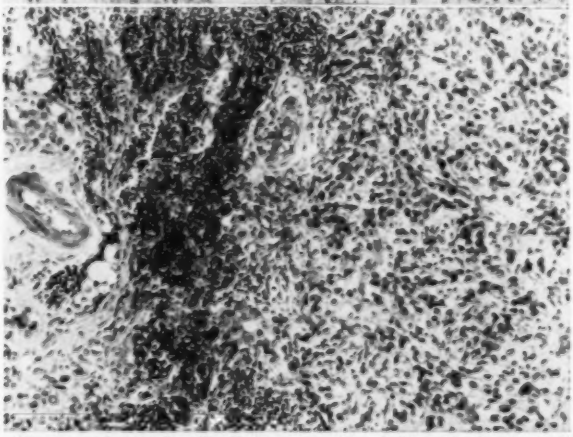

FIGURE 1: Shows polygonal cells lining a cystic cleft and also transition forms to fibroblastic-like cells. X320 **FIGURE 2:** Groups of polyhedral cells lying within a delicate fibrous stroma. X128 **FIGURE 3:** Cellular metastatic deposit in a hilar node. Z128 fibroblastic-like cells. X320

On April 23, 1958, she was seen as an out-patient at the local sanatorium. She was complaining of considerable pain in the left chest, especially on deep inspiration. She had lost 15 pounds in weight, and also complained of pain in the shoulders and knees. Physical examination showed a pale, obviously ill young girl with diminished breath sounds in the left chest posteriorly. Her tuberculin test (1:1,000) was negative. The sedimentation rate was 33 mm. in one hour (Westergren), and chest film revealed considerable pleural thickening over the left base with a suggestion of a small amount of fluid still present in the costo-phrenic angle. A diagnosis of left pleurisy with effusion was made, and it was felt that this was probably tuberculous, although the negative tuberculin test was puzzling.

She was seen again on June 11, 1958, and in the interval had received streptomycin daily. At this time she complained of marked pain on the right side of the chest. It was dull and most bothersome when she took a deep breath. She had a slight cough with a small amount of whitish sputum. She had lost a further three and one-half pounds since the previous examination. There was diminished movement of the left chest with dullness over both bases. Breath sounds were much diminished over both bases. Tuberculin test (1:100) was negative. The sedimentation rate was 40 mm. in one hour (Westergren), hemoglobin 85 per cent, and red blood cell count 5,700,000. Chest films on this date showed a small indistinct shadow with a speck of calcium in its center in the first left interspace. There was still some pleural thickening over the left base, although the costo-phrenic angle was much clearer and the shadow in this area improved. On the right side there was haziness over the base and the outline of the diaphragm was obscured. Her final admission to hospital was on July 6, 1958. X-ray film of the chest on July 7, showed no evidence of effusion at the left base. A large effusion, however, was seen on the right side, and the bronchovascular markings throughout the lung fields were thought to be somewhat prominent. Clinically, it was fairly obvious now that she was suffering from a malignant condition with a collagen disease as an outside possibility. A gastrointestinal series was normal, and gallbladder visualization was negative. L. E. cells were not found. The total proteins were 7.4 gm. per cent, albumin—3.36 gm. per cent, globulin —4.04 gm. per cent. The C reactive protein was 6^{+}. A few days before her death, the hemoglobin was 84 per cent (12.4 gm. per 100 ml.), and hematocrit 41 per cent, white cell count 13,750, and sedimentation rate 55 mm. in one hour. She was treated with antibiotics and meticorten, but her downhill course was progressive with a troublesome cough and respiratory distress. She died on July 22, 1958.

A complete autopsy, except for the head, was performed. The body showed emaciation. The pathological findings were confined to the chest cavity. Both lungs were adherent to the chest wall and were separated with great difficulty leaving many nodules of firm greyish tissue adherent to the thoracic cage. The right dome of the diaphragm was elevated, the right lung being compressed into a small fist-sized area by a bloody pleural effusion of approximately 800 cc. The right pleura measured up to 1.5 cm. in thickness. The right lung weighed 290 grams. The left lung showed a similar appearance with pleural thickening measuring up to

10 cm., being especially prominent over the lateral and posterior aspects. The superior surface of the diaphragm showed numerous superficial areas of infiltration with firm greyish tumor. Serial section through both lungs showed widespread diffuse infiltration with greyish nodules measuring up to 1.0 cm. in diameter. These nodules were especially marked subpleurally, but were also widespread throughout the lung tissue, diminishing in numbers as the hilum of the lung was reached. They appeared predominantly perivascular. The hilar nodes were prominent, but only one showed gross evidence of tumor. The pericardium was not involved. A careful search, especially of the bronchial tree, disclosed no primary tumor elsewhere in the body, nor was there evidence of extrathoracic spread of tumor including sections of vertebrae.

Histological Appearance of Tumor

Sections showed a pleomorphic tumor encasing the lungs and extending into the lung parenchyma in a perivascular distribution. In some situations the tumor consisted of rather closely packed groups of polygonal cells with relatively abundant eosinophilic cytoplasm and irregularly round or oval nuclei having a finely punctuate chromatin structure. Mitotic figures were exceedingly infrequent in all situations. These groups of polygonal cells lay within a fibrous stroma which contained little or no inflammatory infiltrate. In some areas the polygonal cells lined irregular cystic spaces or clefts, but nowhere did the tumor cells form an alveolar or glandular structure (Figures 1 and 2). In other sections transition forms were seen between polygonal cells as previously described and more elongated forms resembling fibroblasts. In some situations on the pleural surface one could observe apparent transitions between non-neoplastic, but hyperplastic mesothelial cells and the type cell of the neoplasm.

The metastatic tumor within the affected hilar node appeared more cellular with less fibrous stroma than the tumor observed elsewhere. In some areas within the lung the perivascular extensions of tumor invaded bronchial walls and became continuous with bronchial epithelium, but nowhere was there any indication that the tumor had actually originated from bronchial epithelium.

Discussion

Recently McCaughey[2] described 11 cases of diffuse mesothelioma. They showed epithelial, mesenchymal, mixed and anaplastic features. His youngest case was aged 40. He reviewed 305 cases of proved pulmonary carcinoma, and in only five of these was the pleura on the affected side heavily infiltrated. Moreover, in none of these 305 cases was the histological picture in any way consistent with that of mesothelioma. He also examined slides from 600 carcinomas from various other locations, and in only one (carcinoma of the thyroid), did the appearance closely simulate a diffuse pleural neoplasm. The great majority of secondary tumor deposits in the pleura form discrete and confluent nodules and do not possess the sheet-like character of diffuse primary pleural neoplasms.

Stout and Murray,[3] and Sano et al,[4] used tissue culture methods as a useful aid in the diagnosis of their cases.

An interesting case of malignant mesothelioma in this instance of the peritoneum in a 42 year-old man has been reported recently by Nesbitt et al.[5] This case was associated with hypoglycemia which was thought to be due to some as yet unknown property of the tumor.

The case reported in this article posed a difficult diagnostic problem. Initially, tuberculosis seemed a likely diagnosis, but it was only in the terminal stages of the illness that the malignant nature of the condition was seriously considered.

The histological appearance of the tumor in many areas taken individually could not be construed as frankly malignant. However, the overall picture, including the perivascular and peribronchial infiltration, and the involvement of a hilar node placed the tumor in the malignant class. A careful, but unproductive search was made for a primary focus in the bronchial tree and elsewhere in the body. This fact, together with the unusual histological appearance which is consistent with previous descriptions for this tumor, is convincing evidence that the case is one of diffuse pleural mesothelioma.

In retrospect, pleural biopsy early in the illness may have indicated the true nature of the disease. It would seem that diagnosis would have to be made extremely early in the course of this condition to hold out any hope of cure, and an early and adequate pleural or lung biopsy in any atypical case of pulmonary disease with prominent pleural thickening would be strongly indicated.

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PREGNANCY AND CONFINEMENT AFTER MITRAL COMMISSUROTOMY

Diseases of the cardiovascular system occupy an important place in obstetrical pathology, and among the causes of maternal mortality, these diseases, especially the mitral disease, quite often take the first place.

In view of the high maternal mortality rate in mitral stenosis (6.2 per cent), obstetricians and internists until recently advised interruption of pregnancy rather than its continuation. Important advances in cardiac surgery opened new and very hopeful possibilities for women suffering from disease of the heart with stenosis predominating, and wishing to have a child.

Experience of Soviet and foreign obstetricians shows that pregnancy and confinement can run a favorable course after commissurotomy performed for mitral stenosis.

Of particular interest are cases of pregnant women who were subjected to commissurotomy and were able to carry the child to full term and have a normal confinement.

Rusin, I. Y.: "Pregnancy after Mitral Commissurotomy," *Chest Surgery*, II:53, 1960.

CLINICO-MORPHOLOGIC OBSERVATIONS OF RESULTS FOLLOWING LIGATION OF THE RIGHT PULMONARY ARTERY IN TUBERCULOSIS

Clinico-morphologic studies are of interest concerning a patient who, after five years following ligation of the right pulmonary artery, had to submit to pneumonectomy for tuberculosis.

The data obtained show the gaseous exchange in the lung where ligation had taken place to be markedly decreased and at the same time, there were indications of the possibility of partial compensation of pulmonary function at the expense of the collaterals between the systems of the pulmonary and the bronchial arteries.

As to the tuberculous process itself, its clinical activity was low and the sclerotic changes dominated over the destructive lesions.

Bendet, Y. A., and Fedotov, A. F.: "Clinico-morphologic Observations of Results following Ligation of the Right Pulmonary Artery in Tuberculosis," *Chest Surgery*, II:99, 1960.

Pulmonary Alveolar Proteinosis, A Case Report

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In 1958, Rosen, Castleman and Liebow[1] reported a series of 27 cases of a pulmonary disease which was characterized by the accumulation of a proteinaceous material in the alveoli. This material, rich in lipid, yields a positive reaction to periodic acid-Schiff stain. It is proposed that it may be produced by large alveolar "septal cells." The authors state:

> "The histologic structures of the lesions in alveolar proteinosis are so characteristic and similar from one case to another that it seems highly unlikely that this could have escaped description previously. Therefore, it is probable either that the prevalence of this condition has increased greatly or that there is a new agent, as yet unidentified, in the environment. Since the lesion is confined to the lungs and perhaps the draining lymph nodes, it appears likely that the causative agent, whether living or inanimate, is inhaled. The nature of the agent can only be conjectured at this time."

Although the etiology of the disease is unknown, the clinical, roentgenographic and pathologic findings are typical enough to warrant the use of the term "pulmonary alveolar proteinosis." Since the original publication appeared, at least two more cases have been recorded.[2,3] It is interesting that this condition bears some resemblance to *Pneumocystis carinii* infection of the lung (interstitial plasma cell pneumonitis), and indeed, Rosen, Castleman and Liebow included in their series several cases previously reported as pneumocystis infection.[4]

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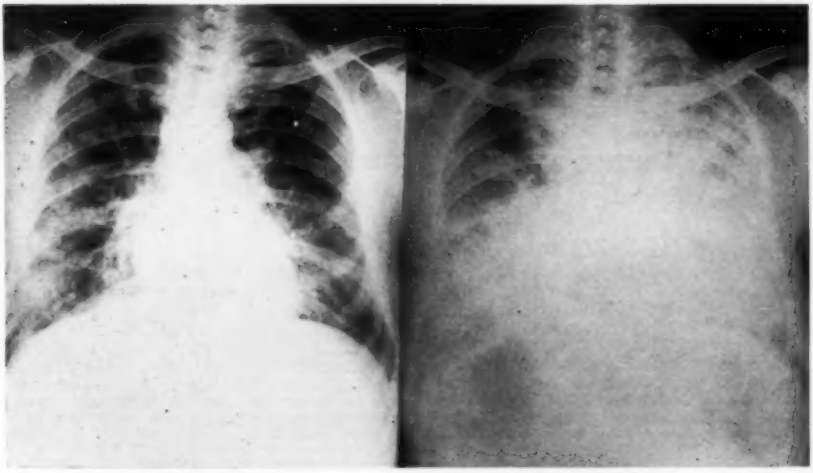

FIGURE 1A FIGURE 1B

FIGURE 1a: Chest x-ray film made in April, 1956. Note bilateral infiltrate, worse on the right. FIGURE 1b: January, 1957. Note severe bilateral process. Film made at hospital admission elsewhere.

The patients thus far reported are primarily men between 20 and 50 years of age, although the range is from 28 months to 57 years. With exclusion of military personnel, two-fifths of the patients are women. There appears to be no geographical predilection since cases have been noted in all parts of the United States, as well as Canada, England, Italy and New Zealand.[1,4]

It is felt that noxious inhalants may play a role in the production of the disease. However, on analysis of occupation and exposure this is by no means a constant finding. Nocardia[1,3] and cryptococcus are considered to be superimposed infectious agents. Tuberculosis was successfully treated in one patient two years before the onset of the proteinosis.†[4] Many of the patients date the onset of their illnesses to pneumonia-like episodes, although the majority note only insidious and progressive dyspnea and cough with varying amounts of sputum. Fatigability, chest pain and weight loss may also be present. Pulmonary symptoms may be minimal and one case presented as a fever of unknown origin.[2] Physical findings, such as rales, clubbing and cyanosis are inconstant. The radiographic changes are rather constant and somewhat similar to those of pulmonary edema with typical perihilar densities. Those usually are far more marked than the clinical state of the patient might lead one to anticipate. Large areas of consolidation may be present. If partial clearing occurs, a diffuse, nodular infiltrate may remain (Fig. 1f).

Observations thus far would indicate three courses that the disease may take. First, complete radiographic and symptomatic remission may occur. Second, the disease may run a chronic course as evidenced by persistence of roentgenographic findings and symptoms, either of which may increase or decrease in severity. Finally, death from respiratory insufficiency or overwhelming superinfection may occur.

Routine laboratory studies are normal save for a possible mild polymorphonuclear leucocytosis and occasional mild polycythemia. Numer-

†Case number 9 in article by Rosen and associates.[1]

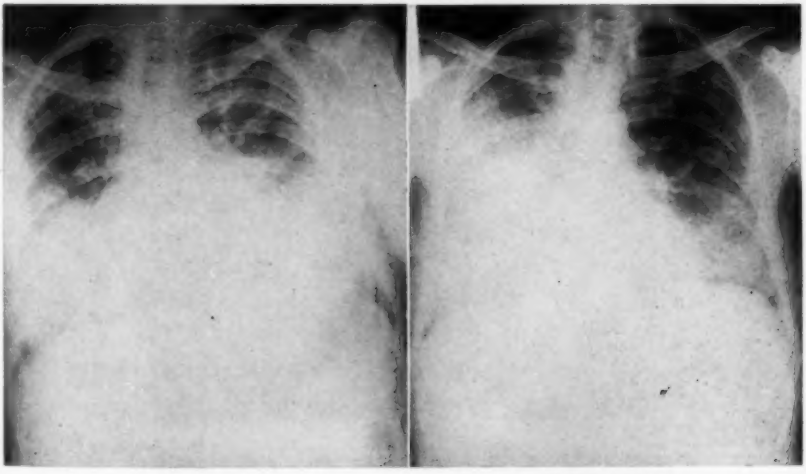

FIGURE 1C FIGURE 1D

FIGURES 1c and 1d: September, 1958 and January, 1958. Films taken during two subsequent acute episodes requiring hospitalization.

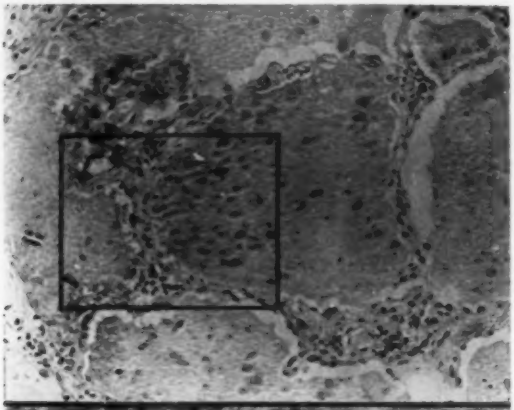

FIGURE 2a

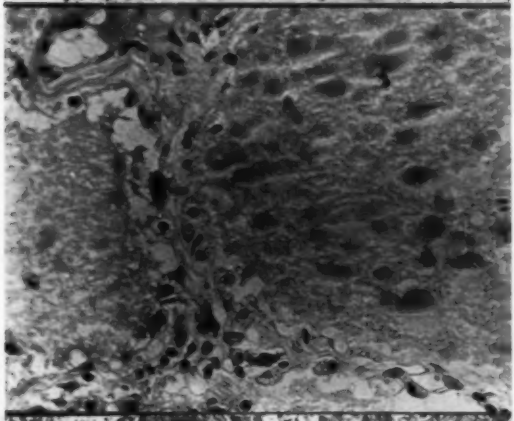

FIGURE 2b

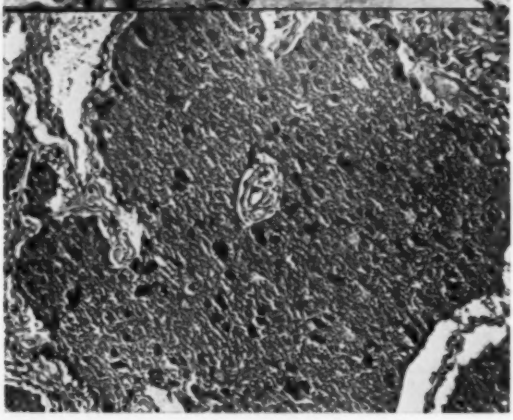

FIGURE 2c

FIGURE 2a: Histologic section with H and E stain, showing proteinaceous material within an alveolus. X 150. **FIGURE 2b:** Higher magnification (area of inset in 2a) showing septal cells containing eosinophilic material. X 400. **FIGURE 2c:** Another alveolus, the content of which is strongly PAS-positive. X 150.

ous cultures of sputum and pulmonary tissue have not been helpful, nor have serologic and skin tests. Pulmonary function studies in advanced cases may reveal evidence of alveolar-capillary block.

At operation for biopsy and at autopsy, the affected areas consist of relatively firm masses from which a milky fluid exudes on gentle pressure. The remaining lung tissue is not remarkable.

Microscopically, the alveoli are filled with eosinophilic proteinaceous material, which is rather homogeneous except for cellular debris. On PAS stain, it assumes a more granular form (Figs. 2a-2c). The material is seen in proliferating "septal cells," which appear to desquamate into the alveoli. This suggests its origin in these cells. There is surprisingly little evidence of inflammation except for minimal lymphocytic infiltration in some bronchiolar walls. Chemical studies have been performed to determine the exact nature of the substance, but so far are not definitive.[1]

Treatment of these patients has employed antibiotics, steroids, broncho-dilators and potassium iodide.[1,3,4] Evaluation of benefit due to these agents is difficult in view of the unpredictable nature of the disease.

Case Report

A 38-year-old white elevator operator entered the New York Veterans Administration Hospital on January 12, 1959 because of slight exertional dyspnea and the history of multiple episodes of "pneumonia." At the time of admission he had no cough, fever or other symptom.

In March of 1956 he was treated because of chest pain with penicillin and bed rest for 10 days. Other details are not known but a chest roentgenogram is available (Fig. 1a). In January, 1957, September, 1958 and again in December, 1958 he was admitted to other hospitals because of fever, chest pain, dyspnea and cough. On each admission he had fever (103-104°F), tachycardia (110-130) and bilateral moist rales. Chest roentgenograms revealed extensive involvement bilaterally (Figs. 1b-1e). His signs and symptoms cleared remarkably quickly on a regimen of antibiotics, oxygen

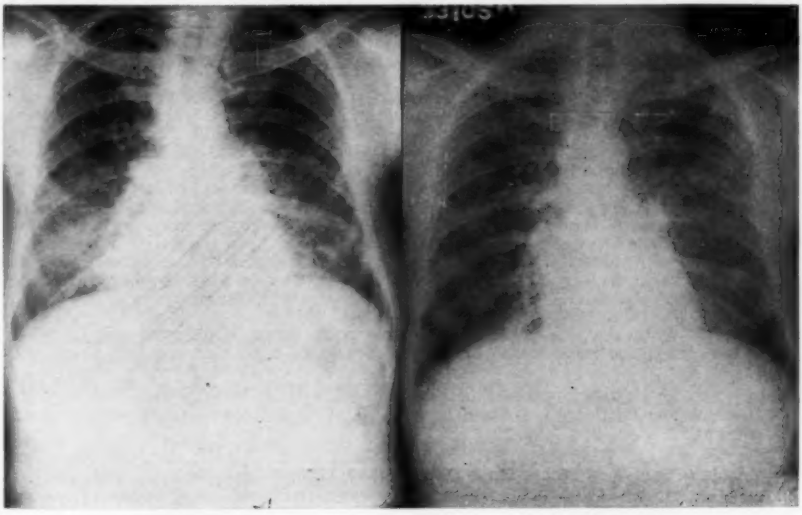

FIGURE 1E FIGURE 1F

FIGURE 1e: Roentgenogram taken eight days after that shown in Fig. 1d. Note rapid resolution and resemblance to Fig. 1a, two years previously. FIGURE 1f: Preoperative film in January, 1959. Note the diffuse, finely nodular infiltrate.

and bed rest. He did not receive digitalis or diuretics. Multiple sputum studies were negative for pathogens including acid-fast organisms.

From 1945 until 1952 he was employed as a power press operator. He fired a coal boiler in the year 1952. Since that time he has been an elevator operator. There was nothing to suggest exposure to noxious inhalants prior to the above episodes.

Physical examination on admission to this hospital revealed a healthy appearing man with a blood pressure of 150/100, pulse of 84 and temperature of 98°F. There was clubbing of the fingers but no cyanosis. Examination of the heart and lungs was negative except for some harsh breath sounds bilaterally. Laboratory studies included a hematocrit of 49 per cent and a hemoglobin of 15.6 gm per 100 ml. The white-cell count was 9600 with a normal differential. The blood urea nitrogen, blood sugar, serum bilirubin, alkaline phosphatase, thymol turbidity, cephalin flocculation, calcium, phosphorus and serum proteins were within normal limits.

Two of four gastric washings grew out acid-fast scotochromogens on culture. One of five sputum cultures grew out two colonies of similar organisms. Guinea pig inoculation was carried out by intraperitoneal injection of 200 million organisms, resulting in death of the animal in seven weeks. Yellow necrotic areas were found in the liver and lung and contained acid-fast bacilli.

Intermediate strength PPD was positive; histoplasmin, coccidiodin and blastomycin skin tests were negative. A scalene node biopsy was not helpful. Chest roentgenograms revealed a diffuse, granular infiltrate bilaterally (Fig. 1f). Arterial oxyhemoglobin saturation at rest was 91 per cent. This rose to 99.5 per cent with the patient breathing 100 per cent oxygen. The carbon dioxide content was 41.5 vols. per 100 ml. Vital capacity was 2.37 liters and maximum breathing capacity 105 liters per minute. (Predicted values 3.75 liters and 110 liters per minute respectively).

On July 19, 1959 a lung biopsy was performed through a left posterolateral thoracotomy. There were no adhesions. The upper and lower lobes were crepitant to palpation except for numerous indurated areas, the largest of which was two centimeters in diameter, was subpleural in location and in the anterior segment of the upper lobe. This was biopsied and a grey-white purulent appearing material exuded from the cut surface. Routine culture, acid-fast smear and culture, and fungus smear and culture (performed on the tissue and liquid material) were all negative.

On histologic section, the alveoli were filled with proteinaceous material which stained with PAS. There was no significant inflammatory reaction (Figs. 2a-2c).**

He was relatively well until August, 1959 when he was again admitted because of fever and an increase in radiographic findings. This, too, responded to non-specific therapy, no antibiotics having been used on this occasion.

Discussion

A case of pulmonary alveolar proteinosis, which has been manifested by numerous acute episodes of a diffuse pneumonic process is presented. The symptoms include fever, chest pain, cough and dyspnea. During quiescent phases there has been only mild shortness of breath. Radiographically, pulmonary edema or consolidation is suggested with marked clearing concomitant with symptomatic improvement. Arterial oxyhemoglobin saturations and ventilatory studies are consistent with a mild alveolar-capillary block.

There is no doubt that the diffuse nodularity seen in the above patient is due to a deposition of the proteinaceous material characteristic of the disease. However, it seems unlikely that the full blown roentgenographic change (Figs. 1b-1d) is due solely to the material since each of the episodes has been consistent clinically with severe, rapidly clearing pneumonitis. On this evidence one can only infer that the pulmonary alveolar proteinosis either sets the stage for the acute episodes, which are otherwise unrelated, or that the episodes are the direct cause of the histologic changes. Against the latter concept is the striking lack of signs of inflammation microscopically; nor have any definite pathogens been consistently recovered from the many patients with the disease. The findings of scotochromogenic acid-fast bacilli in this patient's sputum and gastric washings are thought to be fortuitous, despite the result of guinea pig inoculation, the pulmonary tissue itself having been sterile on culture.

**Dr. Averill A. Liebow, Yale University School of Medicine, kindly reviewed the slides and confirmed the impression that they represented a case of alveolar proteinosis.

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SECTION ON CARDIOVASCULAR DISEASES

Hypothermic Perfusion and Circulatory Arrest for Surgical Correction of Tetralogy of Fallot with Previously Constructed Potts' Anastomosis*

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An aorticopulmonary anastomosis constructed after the manner of Potts and associates[1] is difficult of access by the anterior approach. Such an anastomosis has thus hindered later attempts to correct the tetralogy of Fallot in a one-stage operation. Because in many cases of this type with recurrence of symptoms the only significant source of pulmonary blood flow is the aorticopulmonary anastomosis, a two-stage operation appears undesirable. For this situation, a technic has been devised to facilitate closure of the aorticopulmonary anastomosis at the time of intracardiac correction of the tetralogy.

Technic

The right external iliac artery is exposed extraperitoneally for arterial cannulation. A primary median sternotomy incision is made. The pericardium is incised vertically and wide exposure of the intrapericardial structures is obtained. Only the dissections ordinarily accomplished in preparation for whole-body perfusion are necessary.

Whole-body perfusion, utilizing a Gibbon-Mayo pump oxygenator, is begun as usual.[2,3] The pump oxygenator is equipped with a modified Brown-Emmons heat exchanger located in the line leading from the oxygenator pump to the oxygenator. The temperature of the water circulating through the heat exchanger is controlled by a manually adjustable Powers mixing valve as described by Brown.[4] As soon as extracorporeal circulation is established the temperature of the water circulating through the heat exchanger is reduced to 12° C. Flow rates of approximately 2.4 liters per minute per square meter of body surface are utilized until the patient's esophageal temperature reaches approximately 26 to 28° C. At that time the water temperature is raised to 27° C., the perfusion rate is reduced to approximately 1.5 L./min./sq.m., and preparations are made to begin the definitive procedure.

Whole-body perfusion is discontinued and the ascending aorta is cross-clamped, thus instituting circulatory arrest. The main pulmonary artery (which under these circumstances usually is moderately enlarged) is opened (fig. 1). In the two cases in which this technic has been employed it was easy to visualize the aorticopulmonary anastomosis in the

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left main pulmonary artery through the incision. With a series of interrupted silk sutures the aorticopulmonary anastomosis is closed securely from within the pulmonary artery. Before the last stitch or two are tied, a brief period of perfusion is begun, so that blood is emerging from the aorta while the final tying is done. This circumstance should minimize the possibility that air might be trapped in the aorta and subsequently carried to the brain. As soon as repair of the anastomosis is completed, extracorporeal circulation is re-established at 1.4 L./min./sq.m., temperature in the heat exchanger having been maintained at about 27° C. during the period of circulatory arrest. Normally circulatory arrest should not be needed longer than 10 to 15 minutes for closure of the anastomosis.

Extracorporeal circulation may be continued as a hypothermic perfusion at the reduced rate of flow until the major portion of the intracardiac repair of the tetralogy of Fallot has been accomplished. However, the period of intracardiac repair can be utilized for rewarming of the patient. To accomplish this the water temperature is raised to 38° C., and as the patient's body temperature begins to rise the perfusion rate gradually is increased. When the body temperature nears 33 to 35° C., the water temperature can be advanced to 42° C and the perfusion rate to 2.4 L./min./sq.m. It has appeared advantageous to continue whole-body perfusion and rewarming until the patient's esophageal tempera-

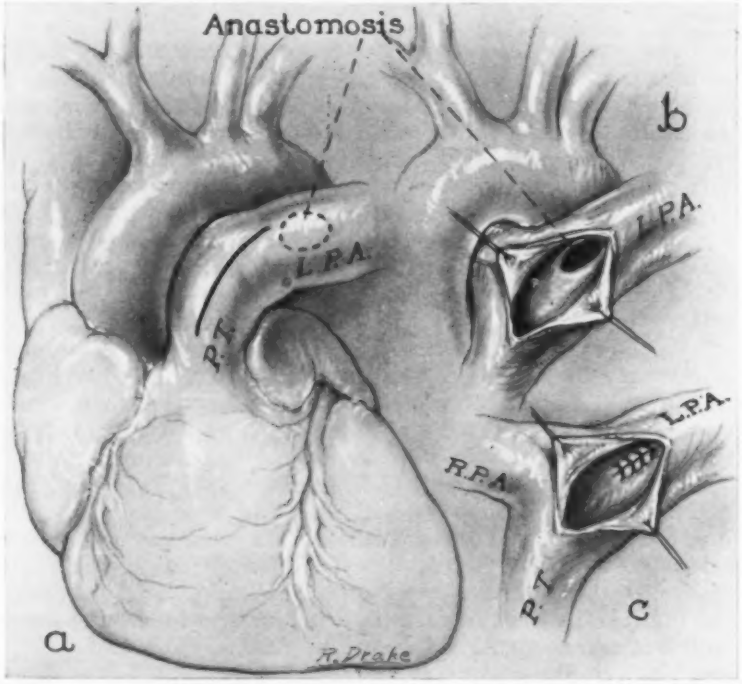

FIGURE 1: Closure of Potts' anastomosis from within the pulmonary artery during circulatory arrest: incision of artery (*a*), exposure of anastomosis (*b*), and closure of anastomosis (*c*). The incision in the artery is closed before proceeding to intracardiac repair.

ture reaches 37 to 38° C. Extracorporeal circulation is discontinued and the remainder of the operation accomplished in the usual fashion.

Report of Two Cases

CASE 1 — A 12-year-old girl was admitted to the Mayo Clinic because of marked cyanosis and significant disability. At the age of 3 years, in another institution, she had undergone construction of a side-to-side (Potts' type) anastomosis of the aorta and left pulmonary artery. After this operation her condition had been improved. By the age of 5 years, however, cyanosis had recurred, accompanied by some symptoms of cardiac failure. Pulmonary valvotomy had been done, and again temporary improvement had ensued.

On her admission to the Mayo Clinic in April, 1959, the patient's weight was 26.6 kg. (59 pounds) and her height 142 cm. (56 inches). The surface area was 1.02 square meters. Cyanosis was marked and there was clubbing of the fingers. Auscultation disclosed a continuous murmur best heard over the left upper anterior aspect of the chest. Hemoglobin measured 18.5 gm. per 100 ml. of blood.

On April 10, 1959, operation was carried out under general anesthesia induced with intravenous administration of thiopental sodium and maintained with nitrous oxide. Succinylcholine was administered intravenously as required to prevent undue movements under light anesthesia. Respiration was controlled by manual hyperventilation. A median sternotomy incision was made. The main pulmonary artery was found to be of moderate size. There was no evidence of flow from the right ventricle into the pulmonary artery. After opening of the heart it was apparent that the pulmonary valve orifice was now completely atretic, and further that infundibular pulmonary stenosis was severe. Dextroposition of the aorta was pronounced. The ventricular septal defect was large and in the typical high position.

The perfusion (details in figure 2) and closure of the anastomosis were accomplished as previously described, and the anomaly was corrected in the usual manner.

Aside from temporary heart block, which appeared on the day after operation and persisted for 48 hours, the patient recovered uneventfully. She was dismissed from the hospital on the twenty-second postoperative day.

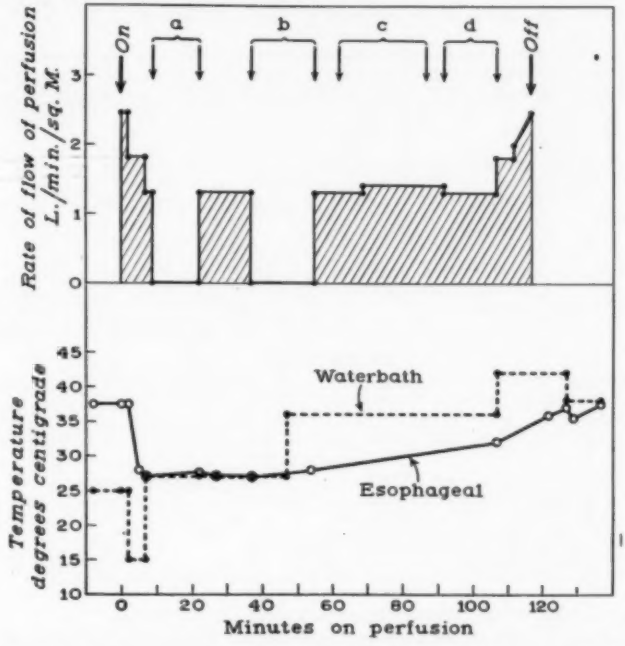

FIGURE 2: Events during perfusion in case 1. The beginning of perfusion is indicated by "on," the end of perfusion by "off." Designated *a* is the period of circulatory arrest during which the aorticopulmonary anastomosis was closed. Designated *b* is a second period of arrest needed for closure of the pulmonary-artery incision. The period of anoxic arrest produced by aortic cross-clamping is marked *c*. The period of total heart-lung bypass following re-institution of cardiac action is marked *d*.

CASE 2 — A 12-year-old boy was brought to the Mayo Clinic because of his increasingly easy fatigability and history of recent cardiac failure.

In June of 1950, when the patient was 3 years of age, a side-to-side aorticopulmonary anastomosis had been established by the Potts technic. After that his symptoms had been considerably improved until approximately 2 years before admission to the clinic. He then had begun to show increasing fatigue and intolerance of exercise, and finally episodic cardiac failure.

On admission to the clinic in May, 1959, the patient was found to weigh 27.3 kg. (60 pounds) and to be 142 cm. (56 inches) tall. The surface area was 1.06 square meters. Blood pressure was 110 millimeters of mercury systolic and 40 diastolic. Cyanosis was noted, and clubbing of fingers and toes. Auscultation revealed a loud continuous murmur over the left upper part of the chest and a rough systolic murmur over the third left interspace. The thoracic roentgenogram revealed marked pulmonary hyperemia and aneurysmal enlargement of the main left pulmonary artery. The electrocardiogram showed marked left ventricular overload with left axis deviation. Review of the electrocardiogram made prior to his original operation revealed that at that time the pattern had been characteristic for the tetralogy of Fallot.

Operation was performed on May 21, 1959. Anesthesia and exposure were accomplished as in case 1. The main pulmonary artery was markedly dilated, as was the aorta itself. Cardiac failure obviously was present, left atrial pressure being 25/15 and right atrial pressure 16/10. Valvular and subvalvular pulmonary stenosis was severe. The ventricular septal defect was large and in the typical high position. Dextroposition of the aorta was unmistakable.

Events during the perfusion (fig. 3) and the operative procedures were as described in the account of case 1.

The patient was awake and in good condition at the end of the procedure, and his convalescence was uneventful. He was dismissed from the hospital on the twenty-first postoperative day.

Comment

Normothermic whole-body perfusion offers acceptable working conditions and excellent support of the patient during many types of intracardiac surgery, but in some situations the operation is rendered difficult by the use of this technic. Among

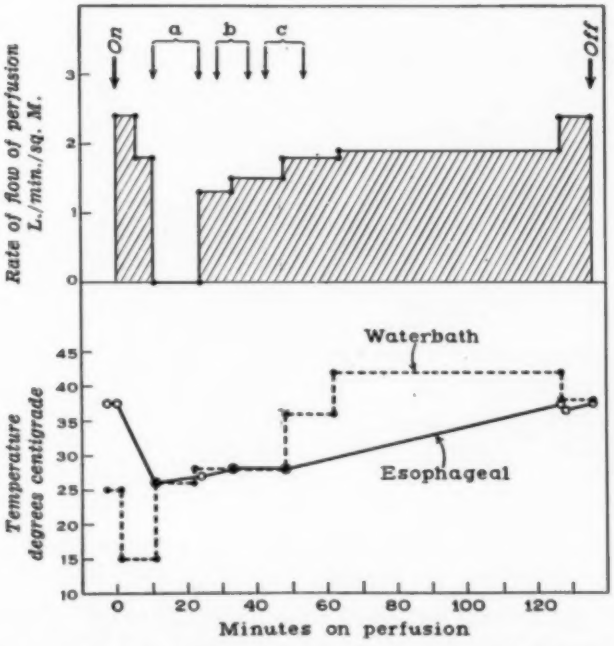

FIGURE 3: Events during perfusion in case 2. In the period designated *a* there was total circulatory arrest. In the periods designated *b* and *c* cardiac arrest was induced by aortic cross-clamping.

these are conditions in which it is necessary to repair a large opening within the aorta, at a site where control of the lips of the aortic opening by a clamp seems not feasible.

Because of the technical difficulty in exposing a previously constructed aorticopulmonary anastomosis from a median sternotomy approach, there appears some advantage in approaching it from within the main pulmonary artery. The ease with which this can be done is surprising. A disadvantage of this approach is that it seems not to give opportunity for disconnecting the aorta and pulmonary artery and repairing the incisions in each, but repair of this fistula from within the pulmonary artery appears satisfactory in spite of this theoretic objection.

Repair obviously cannot be accomplished with the circulation intact. Likewise, if the previously constructed anastomosis is of much size there would be too much hemorrhage from it into the pulmonary artery, were the repair attempted during whole-body perfusion. Stopping of the circulation provides ideal circumstances for this repair.

The combination of hypothermia with extracorporeal circulation has been used and advocated by many since the early work with perfusion technics. Bigelow and coworkers[5] established experimentally the feasibility of circulatory arrest when the body temperature had been lowered. Gollan[6] applied this knowledge to the combination of perfusion and hypothermia and published encouraging results on circulatory arrest in dogs that had been cooled to very low temperatures by means of a pump oxygenator. These efforts culminated in the clinical experience and contributions of Seal and associates.[7] Although there continue to be inadequacies in the knowledge of hypothermic perfusion and circulatory arrest, it does appear — at the least — that relatively short periods of arrest at moderately reduced body temperatures can be accomplished safely.

The technic described herein takes advantage of the surgical simplicity afforded by cessation of the circulation and the knowledge that has been gathered concerning cessation of blood flow at reduced body temperatures. While experience with this technic for operation in patients with the tetralogy of Fallot and previously constructed Potts' anastomosis is limited to two cases, it is anticipated that it will be generally applicable in this situation. If that proves to be so, the use of aorticopulmonary anastomoses as described by Potts[1] for infants severely disabled by tetralogy of Fallot will not be contraindicated by the probable need for later definitive operation.

SUMMARY

A technic is described for repair of a previously constructed aorticopulmonary anastomosis at the time of intracardiac operation to correct tetralogy of Fallot. For this, hypothermic extracorporeal circulation is employed with a brief period of circulatory arrest.

RESUMEN

Se describe una técnica para la reparación de una anastomosis previamente realizada durante la intervención intracardiaca para corregir la tetralogía de Fallot. Para esto se ha empleado la circulación extracorpórea hipotérmica con un período breve de paro circulatorio.

RESUMÉ

Les auteurs décrivent une technique de réparation d'une anastomose aortico-pulmonaire qui avait été pratiquée à l'occasion d'une opération intracardiaque appelée à corriger une tétralogie de Fallot. Ils emploient la circulation extracorporelle sous hypothermie, avec une brève période d'arrêt de la circulation.

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Group A Beta Hemolytic Streptococci and Rheumatic Fever in Miami, Florida:

IV. Correlation Between School Absenteeism, the Isolation of beta Hemolytic Streptococci, and Antistreptolysin O Serum Responses*, **

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Streptococcal "infection" in children may be presumed to have occurred when: (1) there was clinical evidence of the typical illness syndrome, accompanied (2) by the presence of beta hemolytic streptococci in the throat and (3) by a serological response such as an elevation of 2 tubes or greater in the antistreptolysin O titer, in the case of organisms belonging to Lancefield groups A, G, human C and possibly some F strains.[1,2] The absence of any one of these three criteria casts doubts on the existence of true "infection."[2]

One important reason for determining the presence or absence of streptococcal "infections" lies in the relationship presumed to exist between group A organisms and the etiology of rheumatic fever.[4] The isolation of beta hemolytic streptococci from the throats of children has been indicated to be insufficient evidence of itself of "infection," either overt or occult.[3] Furthermore, the presence of antistreptolysin O (ASLO) titer elevation in association with recovery of beta hemolytic streptococci from the throat in the absence of clinical findings also is inadequate to provide positive proof of "infection," and may signify a convalescent carrier state or an "occult" infection.

The present report sets forth data on school absences of children, attending the first three grades of public schools in Miami, Florida, who participated in a throat culture study during the school year, October, 1954 - May, 1955.[6-10] Absences have been related here to the illnesses diagnosed, to the isolation of beta hemolytic streptococci from the throats of these children, and to the ASLO serum titer changes observed concurrently. Tabulations of our data are presented as comparison of *absentee* versus *non-absentee* findings. The *non-absentee* status refers only to children's presence in school during the regularly scheduled days for sampling. Therefore, information on *non-absentees* includes children who were never absent at any time during the school year, as well as those who were present at all culture sessions, but who were absent one or more times between sampling periods (58.3 per cent of the 333 children were in this combined category). The results, therefore, highlight differences between *absentees* and *non-absentees*, but the degree of differences may be lessened by the effects of untabulated absenteeism among the *non-absentee* children.

Throat cultures were taken monthly from the throats of 333 children attending the first three grades of three public schools in Miami, Florida,

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TABLE 1—RELATIONSHIPS OF ASLO FINDINGS, CAUSES OF ABSENCE, AND BETA HEMOLYTIC STREPTOCOCCI RECOVERED FROM THROATS OF CHILDREN FOLLOWING ABSENCE FROM SCHOOL. OCTOBER, 1954-MAY, 1955, MIAMI, FLORIDA.

Cause of Absence			No. of Absences Due to URI*				No. of Absences Due to Unknown Causes*				No. of Absences Due to Other Causes*				Total Number of Absences			
ASLO Responses Following Absence			P‡	A‡	NR‡	Total	P	A	NR	Total	P	A	NR	Total	P	A	NR	Total
Group of beta Streptococci Recovered Some Time During the Year	Beta Streptococci Recovered at Time of Absence																	
No beta Streptococci	No	43	0	0	36	36	0	0	5	5	0	0	16	16	0	0	57	57
Group A beta Streptococci Only	Yes	(20)	2	4+6c†	2	8+6c	1+1c	3+1c	0	4+2c	2	1	0	3	5+1c	8+7c	2	15+8c
	No	(25)	0	2	11	13	0	1	2	3	1	5	7	13	1	8	20	29
	Total	40	2	12	13	27	2	5	2	9	3	6	7	16	7	23	22	52
Group A + Other Groups of beta Streptococci at Same or Different Occasions	Yes	(16)	1Ac	1A, 1Ac 1Bc 2Cc 1Gc	2Ac	1A, 4Ac 1Bc 2Cc 1Gc	1Ac	1Ac 1C 1G 1Gc	0	2Ac 1C 1G 1Gc	1A	1A, 1Ac 2G	0	2A, 1Ac 2G	1A, 2Ac	2A, 3Ac 1Bc 1C, 1Cc 3G, 2Gc	2Ac	3A, 7Ac 1Bc 1C, 2Cc 3G, 2Gc
	No	(15)	1	7	1	9	0	5	0	5	1	4	1	6	2	16	2	20
	Total	25	2	13	3	18	1	9	0	10	2	8	1	11	5	30	4	39
Total Group A beta Streptococci	Yes	(36)	3	12	4	19	3	5	0	8	3	3	0	6	9	20	4	33
	No	(40)	1	9	12	22	0	6	2	8	2	9	8	19	3	24	22	49
	Total	65	4	21	16	41	3	11	2	16	5	12	8	25	12	44	26	82
Group B Strep Only	No and Total	1	0	2	0	2	0	0	0	0	0	1	0	1	0	3	0	3
Group C Strep Only	Yes	(7)	0	1c	0	1c	2c	1+2c	0	1+4c	1	0	0	1	1+2c	1+3c	0	2+5c
	No	(9)	0	4	2	6	0	2	1	3	0	1	0	1	0	7	3	10
	Total	14	0	5	2	7	2	5	1	8	1	1	0	2	3	11	3	17
Group F Strep Only	Yes	(1)	0	2	0	2	0	0	0	0	0	0	0	0	0	2	0	2
	No	(4)	0	0	2	2	0	1	1	2	0	0	1	1	0	1	4	5
	Total	4	0	2	2	4	0	1	1	2	0	0	1	1	0	3	4	7
Group F Strep Only	Yes	(3)	0	1+1c	0	1+1c	0	0	0	0	1	1c	0	1+1c	1	1+2c	0	2+2c
	No	(3)	0	1	1	2	0	1	0	1	0	0	0	0	0	2	1	3
	Total	5	0	3	1	4	0	1	0	1	1	1	0	2	1	5	1	7
More Than One Group of Streptococci at Same or Different Times, but No Group A	Yes	(3)	0	1B NG, F 1Cc/G	1G/Cc	1B 1Cc 1G	0	1Cc/G	0	1Cc	0	1Gc/F	1F/G	1Gc 1F	0	1B 2Cc 1Gc	1Gc 1F	1B, 2Cc 1F, 2Gc
	No	(5)	0	0	1/C, F	1	0	0	0	0	0	1 B, F, NG 2/C, G	2/F, G	5	0	3	3	6
	Total	7	0	2	2	4	0	1	0	1	0	4	3	7	0	7	5	12
Totals, All Absences, with and without Streptococci	Yes	(50)	3	23	5	31	5	12	0	17	5	7	1	13	13	42	6	61
	No	(105)	1	16	54	71	0	10	9	19	2	14	27	43	3	40	90	133
	Total	139	4	39	59	102	5	22	9	36	7	21	28	56	16	82	95	194

*URI=Upper Respiratory Infections, including colds, sore throats, coryza, bronchitis, tonsillitis, "virus infection."
Unknown Causes=Causes that could not be determined from the parents.
Other Causes=Chicken pox, sunburn, and non-medical causes.
‡P=ASLO rise of 2 tubes or more within 6 weeks; A=Absent 2-tube rise; NR=Not recorded.
†c=Continuous, i.e., organisms present on 1 or more occasions before, and during absence. Example: 4c=4 absences associated with Group A organisms, in each of which the Group A organisms had been present on one or more occasions prior to, as well as during the absence.
A, B, C, F, G=Corresponding groups of beta hemolytic streptococci.
NG=Beta hemolytic streptococci, non-groupable.
Fractions=Example 1: NG, F indicates that 1 child was absent, and a Group B streptococcus was recovered at the time of absence; non-groupable and Group F strains were recovered at other times from the same child.
Example 2: 1G/Cc indicates that a group G streptococcus was isolated at the time of absence; at other times, a Group C organism was recovered repeatedly.
Example 3: 1/C, F indicates that 1 child was absent and no beta hemolytic streptococci were recovered during the absence, although Group C and Group F organisms were isolated at other times from the same child.

for eight months from October, 1954 through May, 1955.[8] An initial (October, 1954) and final (May, 1955) venous blood sample was obtained from each child, for ASLO titer determinations.[9] Every time a beta hemolytic streptococcus was isolated from the throat of a child, additional throat cultures and blood samples were taken 2, 4, 8, 16, and 32 weeks later, for the duration of the study. The details of the bacteriological and serological procedures have been described previously.[3,6-10]

Whenever a child was absent from school at the time regularly scheduled for throat swabbing, either at the monthly or bimonthly period, the cause of absence was sought and every effort was exerted to obtain specimens from such a child within 72 hours of the day of absence. In the case where the child returned to school within a day or two after an absence, a throat culture and blood sample were obtained from him in school by a supplementary visit to that school by one of our technical personnel; otherwise the technician went to the child's home to do throat swabbing and collect venous blood from the absentee. Most parents were cooperative and permitted home visits. The "ill" child was not always at home, nor was it possible to obtain accurate clinical diagnosis in every case, since, in many illnesses no physician was in attendance.

No attempt was made to get additional specimens from those children who were absent between regularly scheduled sampling periods.

Results

Of the 333 children participating in the study, 139 were absent on a regularly scheduled sampling day one or more times during the eight-month school year, October, 1954 through May, 1955. Thirty-one children were absent twice, 10 three times, and four four times. Sixty-five of the 139 absentees (46.8 per cent) had group A organisms recovered from their throats, while throat cultures from 72 of 194 children (37.1 per cent) who were never absent from school at scheduled throat-swabbing times, yielded these organisms.

Table 1 presents a more detailed correlation among culture findings, ASLO titer responses, and causes of absenteeism. Of the 102 absences (in 89 children) attributed to upper respiratory infections (including colds, sore throats, tonsillitis, bronchitis, influenza, etc.) ASLO rises of 2 tubes or more were observed in four, failed to occur in 39, and were not recorded in the remaining 59 instances. Absences for which no reasons could be determined from the parents or from the school, were accompanied by titer rises in five instances and no such rises in 22. Where absences were known to be due to conditions other than respiratory illnesses (chicken pox, sunburn, or completely non-medical reasons), seven absences were associated with a rise in ASLO titer and 21 were not. Of 194 total recorded absences, beta hemolytic streptococci were recovered in 61 instances and not recovered in 133. Of the 61 streptococcus-positive absences, 13 were accompanied by ASLO responses, 42 were not, and six were not recorded; 23 (6 per cent) of recorded titers were elevations. In contrast, only three of 43 absences (7 per cent) where no beta hemolytic streptococci were recovered at the time of absence, showed subsequent ASLO responses. When only Group A beta hemolytic streptococci are considered, nine of 29 absences (31 per cent) were accompanied by rises

in ASLO titers. ASLO responses occurred with Group B organisms in none of three absences; with Group C, in three of 14; with Group F, in none of three, and with Group G, in one of six absences. Careful follow-up of all absences indicated that antibiotics were administered only rarely. In every instance, throat swabs were obtained, before medication with antibiotics.

Colony counts were recorded for all beta hemolytic streptococci recovered during absences. Of the 61 recorded absences associated with beta hemolytic streptococcal recovery, 49 (80.3 per cent) yielded less than 25 colonies on original plates. In 45 of the 49, ASLO titers were recorded within six weeks of isolation of organisms. Nine (20 per cent) of these 45 were accompanied by ASLO rises of 2 tubes or more, while 36 (80 per cent) were not. Initial plate colony counts were 25 or more in 12 of the 61 absences (19.7 per cent). ASLO data were available in 10 of the 12, and four of the 10 showed ASLO titer rises of 2 tubes or more.

TABLE 2—COLONY COUNTS OF BETA HEMOLYTIC STREPTOCOCCI RECOVERED DURING OR WITHIN 72 HOURS OF CHILDREN'S ABSENCES FROM SCHOOL, RELATED TO CAUSES OF ABSENCES AND TO ISOLATION OF LANCEFIELD GROUPS OF BETA HEMOLYTIC STREPTOCOCCI. OCTOBER, 1954 - MAY, 1955, MIAMI, FLORIDA.

		Beta Hemolytic Streptococci Recovered											
		Group A†		Group B		Group C		Group F		Group G		TOTALS	
Causes of Absence	Colony Count	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent	No.	per cent
Not Absent at Time of Sampling	1— 4	209	41.8	17	42.5	76	39.2	29	74.4	57	45.2	388	43.2
	5—24	182	36.4	18	45.0	58	29.9	7	17.9	41	32.5	306	34.0
	25—99	50	10.0	2	5.0	24	12.4	2	5.1	8	6.3	86	9.6
	100+	59	11.8	3	7.5	36	18.6	1	2.6	20	15.9	119	13.2
	Total	500	—	40	—	194	—	39	—	126	—	899	—
Upper Respiratory Infection	1— 4	5	26.3	2	100.	3	75.0	1	50.0	3	75.0	14	45.2
	5—24	10	52.6	0	—	0	—	1	50.0	0	—	11	35.5
	25—99	2	10.5	0	—	1	25.0	0	—	0	—	3	9.7
	100+	2	10.5	0	—	0	—	0	—	1	25.0	3	9.7
	Total	19	—	2	—	4	—	2	—	4	—	31	—
Unknown Causes	1— 4	4	50.0	0	—	3	42.9	0	—	1	50.0	8	47.1
	5—24	2	25.0	0	—	2	28.6	0	—	1	50.0	5	29.4
	25—99	1	12.5	0	—	0	—	0	—	0	—	1	5.9
	100+	1	12.5	0	—	2	28.6	0	—	0	—	3	17.6
	Total	8	—	0	—	7	—	0	—	2	—	17	—
Other Causes (Medical & Non-Medical)	1— 4	3	50.0	0	—	0	—	1	100.	4	80.0	8	61.5
	5—25	1	16.7	0	—	1	100.	0	—	1	20.0	3	23.1
	25—99	1	16.7	0	—	0	—	0	—	0	—	1	7.7
	100+	1	16.7	0	—	0	—	0	—	0	—	1	7.7
	Total	6	—	0	—	1	—	1	—	5	—	13	—
GRAND TOTALS	1— 4	221	41.5	19	45.2	82	39.8	31	73.8	65	47.4	418	43.5
	5—24	195	36.6	18	42.9	61	29.6	8	19.0	43	31.4	325	33.9
	25—99	54	10.1	2	4.8	25	12.1	2	4.8	8	5.8	91	9.5
	100+	63	11.8	3	7.1	38	18.4	1	2.4	21	15.3	126	13.1
	Total	533	—	42	—	206	—	42	—	137	—	960*	—

*2 non-groupable colonial recoveries not included in table. Both were in non-absentees and had less than 5 colonies each.

†Wherever more than one group of organisms were recovered from 1 child at the same or different times, tabulation was carried in each of the appropriate streptococcal groups at the time of recovery.

NOTE: This table includes all streptococcal isolates collected at both monthly and mid-monthly periods.

Analyses of colony counts of beta hemolytic streptococci on initial plates (Table 2) are presented for children who were present at each regularly scheduled throat swabbing period, as well as those children who were absent. The findings were subdivided according to Lancefield Groups of streptococci recovered and as to numbers of colonies observed on the initial plate showing the higher count of each pair of plates. Absences due to upper respiratory infections were associated with colony counts of one to 24, in 15 of 19 instances (78.9 per cent) where Group A streptococci were isolated; colony counts of this size were found in 391 of 500 (78.2 per cent) Group A streptococcal isolates where the children were not absent from school at the time of throat culturing. In both the respiratory absentee and the non-absentee categories, colony counts of 25 to 99, and 100 and over were observed in approximately the same proportions.

An "epidemic" of type 6, Group A beta hemolytic streptococci was observed in February, 1955. The isolation of type 6 organisms for the first time from the monthly throat cultures of several children suggested the possibility of an "epidemic." These organisms were recovered from the throats of children, all of whom attended one of two first-grade classes in one school. Throat swabbing was performed on the children present in each of these two classes, on March 16, 1955. Children who were not participating in the regular studies as well as those who were, had throat cultures taken. Of 66 children attending the two classes, five refused permission, 10 were absent, and 51 had their throats swabbed (Table 3). Of the 10 children absent, two were ill with mumps, two with chicken pox, one with an upper respiratory infection and the other five were absent for unexplained reasons. Nineteen of the 51 throat cultures (37.3 per cent) were positive for type 6 streptococci, while 32 (62.7 per cent) were negative. Data on the 51 children as to absence from school were tabulated according to illness after February 1, due to respiratory in-

TABLE 3—ABSENTEE DATA AND THROAT CULTURE FINDINGS (March 16, 1955) ON 51 CHILDREN IN TWO CLASSES AFFECTED BY "EPIDEMIC" OF GROUP A, TYPE 6 BETA HEMOLYTIC STREPTOCOCCI.

				Group A type 6 beta Hemolytic Streptococci Isolated History of Absences: Due to U.R.I.							Group A type 6 beta Hemolytic Streptococci not Isolated History of Absences: Due to U.R.I.						
	Number of Children Absent	Number of Children Who Refused	Number of Children Cultured	2/1-3/15	1/1-2/1	1/1-2/1 and 2/1-3/15	Unknown	Total	No History of Absence 1/1-3/15	Total Children with A_β	2/1-3/15	1/1-2/1	1/1-2/1 and 2/1-3/15	Unknown	Total	No History of Absence 1/1-3/15	Total Children without A_β
Classroom I 32 Individuals	3	5	24	3	1	3	1	8	3	11	2†	1†	2	1	6	7	13
Classroom II 34 Individuals	7	0	27	0	1	0	3	4	4	8	9#	0	1	4	14	5‡	19
Total 2 Classes 66 Individuals	10*	5	51	3	2	3	4	12	7	19	11	1	3	5	20	12	32

*2 children were ill with chicken pox, 2 with mumps, 1 with upper respiratory infection ,5 were not recorded.

†1 child in each category had non-typable Group A beta hemolytic streptococci.

#1 child had non-groupable beta hemolytic streptococci.

‡1 child had Group C beta hemolytic streptococci

fection; illness between January 1 and February 1, of respiratory origin; respiratory infections in each of these two periods; and absences for which causes were not recorded. Of the 19 children who harbored type 6 organisms, 12 (63.1 per cent) had absences listed in one of these categories; of 32 children from whose throats Group A, type 6 streptococci were not isolated, 20 (62.5 per cent) fell into similar categories. During the period from January through March 1955, the absentee rates in the two affected classes were not higher than previously, nor were the rates higher in these classes than in the other classes of the school. The rate of absence for the school was approximately the same as during other months, and this school was among those having low rates in Dade County.

Discussion

Throat swabbing and blood sampling performed during or shortly after their absences, on children attending the first three grades of three public schools and participating in a long-term streptococcal epidemiological project, showed no consistent correlations between absenteeism and (1) rate of isolation of Group A beta hemolytic streptococci, (2) ASLO titer and serial changes in titer, and (3) colony count on original bacterial plates.

The data on absentees included clinical diagnoses in most instances. When respiratory illnesses were considered, Group A streptococci were isolated from 58.5 per cent of children (38 of 65) suffering from upper respiratory infections (colds, virus infections, bronchitis, and so forth) while no beta hemolytic streptococci could be recovered from 67.4 per cent of another group of children absent because of these illnesses (29 of 43). When no respiratory illness and no absenteeism were recorded, 37.1 per cent of the children (72 of 194) were found to be carrying Group A organisms. Thus a higher percentage of absentees harbored Group A streptococci than did children not absent on sampling dates. Among those children who were absent, beta hemolytic streptococci of various groups were recovered more frequently in the presence of respiratory illness (60.4 per cent) than in its absence (39.6 per cent). When an "epidemic" of Group A, type 6 beta hemolytic streptococci occurred no increase in absences due to respiratory illness was recorded.

Respiratory illnesses, when associated with school absences were accompanied by rises in ASLO titers at the time of, or within four weeks after the isolation of Group A beta hemolytic streptococci, in only three of 15 recorded instances (Table 1). Thus when clinical and bacteriological evidence of streptococcal infection was present, only 20 per cent of the cases met the third criterion,[3] immunological response, for such infection. Numbers of children absent from whom other groups of beta hemolytic streptococci were recovered, were too small to permit detailed analysis.

Colony counts of beta hemolytic streptococci on original throat culture swab plates were made because (nose or) throat cultures in which these organisms predominate are considered evidence of preceding beta hemolytic streptococcal infection, evidence which constitutes a minor criterion for the diagnosis of acute rheumatic fever.[11] Study of school absences, presumably due to respiratory illnesses, in relation to colony counts (Table 2) indicated that there were approximately the same percentages of counts over 25 colonies in this category, as there were in the group of absences due to non-respiratory and unknown causes. Percentages were approximately the same when no absences were recorded. Thus, in these investigations, no greater numbers of colonies were observed whether or not clinical respiratory illness sufficient to cause school absence was present. On the other hand, ASLO titer elevations were demonstrable in a larger percentage of absentees from whose throat swabs there were colony counts of over 25, than of absentees with counts of under 25, when Group A beta hemolytic streptococci were isolated. Instances in which counts were over 25 were few, however, and too much weight cannot be placed on the significance of this observation. We would like to call attention, however, to the fact that colony counts of 100 and over were observed in approximately equal percentages from both the non-absentee and upper respiratory absentee groups of children, and that these figures represented only 10 to 12 per cent of the children from whose throats Group A beta hemolytic streptococci were isolated.

Our findings in the present report give no consistent evidence of correlation between absences due to respiratory illnesses and (1) frequency of isolation of beta hemolytic streptococci or of Group A beta hemolytic streptococci; (2) frequency of elevations in ASLO titers; (3) colony counts on original isolation plates; and (4) an "epidemic" of type 6, Group A streptococci.

We have observed: (a) elevated average ASLO titers and indices amongst those children from whose throats Group A streptococci were isolated, (b) a generally low school absentee rate due to upper respiratory infection, and (c) colony counts of

Group A streptococci of a magnitude of 25 colonies or less in approximately 75 per cent of the school absentees studied. We believe that this association of facts reflects a situation in which the host-organism relationship is such that either the host, although responding serologically to the organisms, is relatively resistant to illness caused by Group A beta hemolytic streptococci, or the organisms encountered during our study were of a low order of virulence.

SUMMARY

1. Of 333 children attending the first three grades in three public schools in Miami, Florida, October, 1954 to May, 1955, 139 were absent one or more times during regularly scheduled monthly throat swabbing periods.
2. The reason for each absence was recorded and the throats of these absentees were swabbed as soon as possible (usually within 72 hours).
3. No direct relationship between frequency of isolation of Group A beta hemolytic streptococci and absences could be determined.
4. ASLO levels and responses showed no marked correlation with absenteeism, whether or not Group A organisms were recovered.
5. Colony counts of 25 to 100, and over 100 of Group A beta hemolytic streptococci were found on throat swab culture plates with the same relative frequency in cultures taken from non-absentees as from absentees.
6. No child in our investigation developed a known acute episode of rheumatic fever or glomerulonephritis.
7. School absenteeism, in the present investigation, did not reflect upper respiratory illness in the children found to be carrying beta hemolytic streptococci in their pharynges and manifesting ASLO titer elevations. The relationship of beta hemolytic streptococci to illness has been discussed from the viewpoint of host-organism interaction.

RESUMEN

1. De 33 niños que asisten a los tres primeros años en tres escuelas públicas de Miami, Florida de Octubre de 1954 a Mayo de 1955, hubo 139 que faltaron una o más veces durante los exámenes de tomas de frotis de garganta que se hicieron mensualmente.
2. La razón de cada falta de asistencia se investigó y las gargantas de estos faltistas se sujetaron a la toma de frotis con torunda tan pronto como fué posible (generalmente dentro de 72 horas).
3. No se encontró relación directa entre el aislamiento del estreptococo beta hemolitico grupo A y las faltas.
4. Los niveles de ASLO y la respuesta no mostraron correlación con las ausencias ya se encontraran o no gérmenes del grupo A.
5. Las colonias con cuenta de 25 a 100 o más de 100 del estreptococo beta hemolitico grupo A, se encontraron en los cultivos de garganta, con la misma frecuencia relativa en cultivos de faltistas como de puntuales.
6. Ningún niño en nuestra investigación presentó un episodio conocido de fiebre reumática o de glomerulonefritis.
7. Las faltas a la escuela según esta investigación no se debían a afecciones respiratorias superiores en los niños que se encontró tenían estreptococo beta hemolítico en la faringe y con título de ASLO elevado. La relación del estreptococo hemolítico con la enfermedad se discute desde el punto de vista de las interacciones entre el germen y el huésped.

RESUMÉ

1. Sur 333 enfants fréquentant les cours des trois premiers degrés dans trois écoles publiques à Miami (Floride) d'octobre 1954 à mai 1955, 139 furent absents une ou plusieurs fois pendant les périodes mensuelles régulièrement prévues pour faire des prélèvements laryngés.
2. La raison de chaque absence fut enregistrée et la gorge de ces absents fut écouvillonnée aussi tôt que possible (habituellement moins de 72 heures après l'absence).
3. Aucune relation directe ne put être déterminée entre la fréquence d'isolement de streptocoques hémolytiques beta du groupe A et les absences.
4. Les taux et les réponses des antistreptolysines O ne montrèrent aucune corrélation nette avec l'absentéisme, que l'on ait constaté ou non des germes du groupe A.
5. On trouva un nombre de colonies de 25 à 100 et d'autres de plus de 100 pour les streptocoques hémolytiques beta du groupe A, à la culture des prélèvements laryngés, avec la même relative fréquence pour les cultures faites chez les enfants qui avaient été absents que chez ceux qui ne l'avaient pas été.
6. Pendant notre investigation aucun enfant ne fit d'épisode aigu connu de rhumatisme articulaire ou de glomérulonéphrite.
7. L'absentéisme escolaire, dans la présente étude, ne reflèta aucune atteinte respiratoire particulière chez les enfants porteurs de streptocoques hémolytiques beta dans leur pharynx et ayant une élévation des antistreptolysines O. La relation entre streptocoques hémolytiques beta et la maladie a été discutée du point de vue de l'interaction entre le microbe et l'individu qui l'héberge.

ZUSAMMENFASSUNG

1. Von 333 Kindern, die die ersten 3 Klassen der drei öffentlichen Schulen in Miami in Florida zwischen Oktober 1954 und Mai 1955 besuchten, fehlten 139 ein oder mehrere Male im Verlauf von regelmässig festgesetzten Terminen für monatliche Halsabstriche.

2. Der Grund für jedes Fehlen wurde ermittelt und der Halsabstrich bei diesen Kindern sobald als möglich nachgeholt (gewöhnlich innerhalb von 72 Stunden).

3. Es konnte keine direkte Beziehung ermittelt werden zwischen der Häufigkeit, mit der beta-hämolytische Streptokokken der Gruppe A gefunden wurden und dem Fehlen in der Schule.

4. ASLO-Werte und Reaktionen zeigten keine ausgesprochene Beziehung zu dem Fernbleiben, unbeschadet dessen, ob Erreger der Gruppe A gefunden wurden oder nicht.

5. Auszählung von Kolonien zwischen 25 und 100 und über 100 der beta-hämolytischen Gruppe A fanden sich auf Kulturplatten von Halsabstrichen mit derselben relativen Häufigkeit in Kulturen von Kindern, die nicht gefehlt hatten, und solchen, die ferngeblieben waren.

6. Bei keinen Kind unserer Untersuchungsreihe entwickelte sich ein akutes Stadium eines rheumatischen Fiebers oder eine Glomerulonephritis.

2. Das Fernbleiben von der Schule war in der vorliegenden Untersuchung kein Spiegelbild einer Erkrankung der oberen Luftwege unter Kindern, bei denen sich herausgestellt hatte, daß sie in ihrem Hals beta-hämolytische Streptokokken beherbergten und ASLO-Titersteigerungen aufwiesen. Diskussion über die Beziehung von beta-hämolytischen Streptokokken zu Krankheiten vom Standpunkt der Wechselwirkung zwischen Wirt und Keim.

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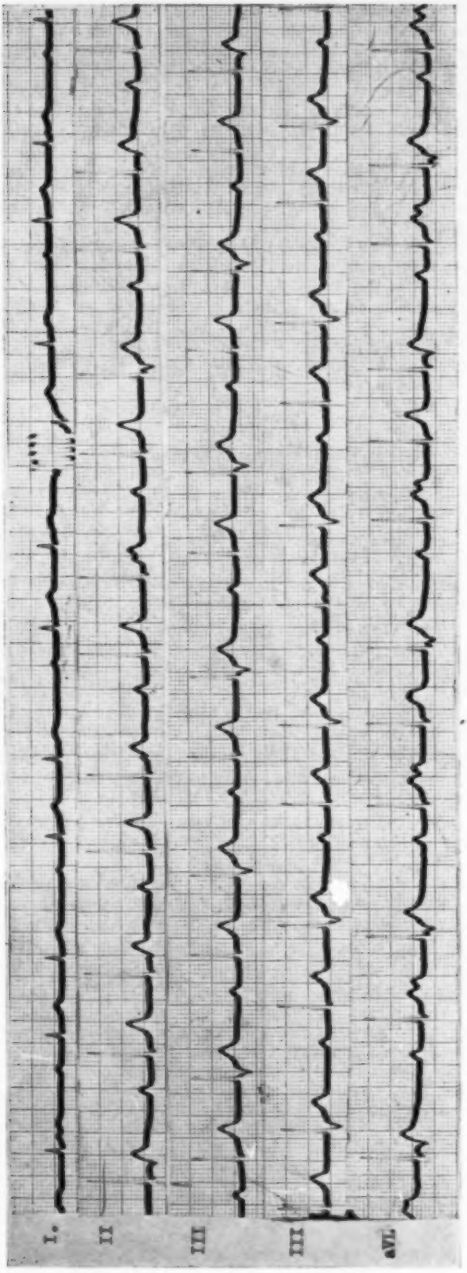
ELECTROCARDIOGRAM OF THE MONTH

Edited by Stephen R. Elek, M.D.

A-V Nodal Extrasystoles



These tracings were obtained from a 17-year-old patient with active rheumatic fever. There was no valvular lesion. No digitalis had been given.

The top three tracings are Leads I, II and III, in that order. Then Lead III is repeated. The bottom tracing is aVL, obtained the next day.

The analysis of this unusual arrhythmia best begins with the fourth strip (Lead III). In constant repetition we see a sinus beat with a P-R interval of 0.34 second followed by another beat conducted with a P-R interval of 0.48 second. The second conducted beat has an inverted wave which follows the R wave and rather resembles a broad S wave. However, slight irregularities in the configuration of this wave suggest that it is really an inverted P following the QRS complex. The top three tracings support this contention since this wave often appears later between QRS and T, showing that it is not part of the ventricular complex. Also, in the center of the second strip (Lead II) this inverted P wave is missing and two typical groups caused by periodically dropped beats (Wenckebach periods) can bee seen. Elsewhere in the tracing the inverted P wave appears after every second and third ventricular complex.

Low, positive P waves in Lead I with deeply inverted, peaked P waves in Leads II and III are typical for atrial contractions originating in the A-V node. We are therefore dealing in these tracings with two disturbances of rhythm, periodically dropped beats and A-V nodal extrasystoles. The latter are blocked on their way to the ventricles; the QRS complex after which they appear is a conducted sinus beat: its P wave is buried in the T of the preceding ventricular complex. The coupling of the extrasystoles, that is the distance between the extrasystole and the preceding P wave, is about 0.52 second. While this interval is fairly constant, the length of the P-R interval of the conducted beats varies. Thus the extrasystoles appear at varying times after the QRS complex.

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The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

X-RAY FILM OF THE MONTH

Edited by Benjamin Felson, M.D.

FIGURE 1

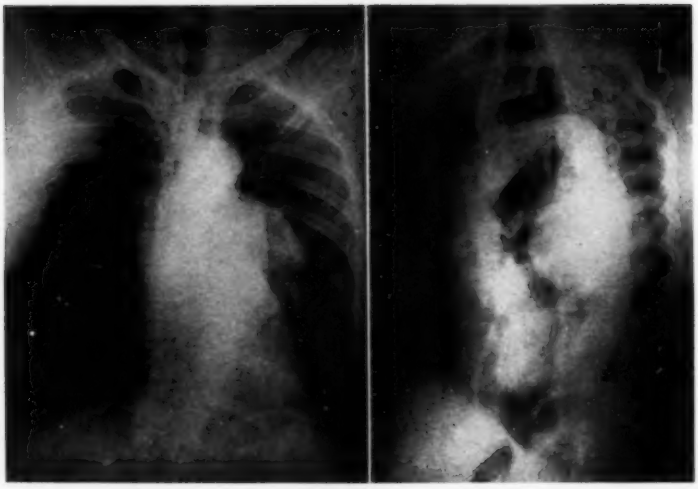

FIGURE 2

A colored man, aged 47, who had gonorrhea 23 years ago, but lues was denied.

One year ago, had what he described as pleurisy on the left side. Present pain is similar to that of one year ago. No other diseases or injuries.

Present complaint is pain on right side of chest and lower dorsal spine for the past four to six weeks. Pain has been constant for the past four weeks; worse on inspiration. Slight cough, no expectoration and no hemoptysis. No acute infection.

Physical examination revealed a well developed, well nourished colored man, who is making an effort to splint his right side. His blood pressure was 130/85. Pupils react to light and accommodation. Heart sounds normal. Lungs normal. Palpation of dorsal spine reveals a localized area of tenderness over D 10. Wassermann one year was negative.

X-ray examination reveals a large circular mass in the posterior mediastinum, encroaching upon the left pulmonic field. The trachea is displaced anteriorly, and the left main bronchus is compressed and elevated. The left pulmonary artery is elevated and surrounds the mass.

Answer: Segmental Dilatation of Aorta.

Angiocardiographic examination reveals a huge segmental dilatation in the descending aorta, with no evidences of coarctation.

HENRY K. TAYLOR, M.D.
New York, New York

The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with brief history. Please submit material to: Benjamin Felson, M.D., chairman, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

CLINICAL APPLICATION OF CORONARY ANGIOGRAPHY

Coronary angiography has been used as a routine investigation to obtain additional information regarding the blood supply to the myocardium. It was possible to make a partial check of the angiographic findings at operation. No important discrepancy was detected. It is therefore considered that this is a reliable and safe procedure that should be carried out when additional information is required concerning the coronary circulation. In patients with aortic valve disease, it may be important to know the state of the coronary circulation before deciding on the advisability or type of operation to be performed.

Visualization of the coronary circulation might assist in the diagnosis of chest pain when the electrocardiogram is found to be normal. The demonstration of completely normal major coronary vessels would greatly assist the physician in his management.

Sloman, G., and Hare, W. S. C.: "Clinical Application of Coronary Angiography," *Med. J. of Austral.*, 2:16, 1960.

ACQUIRED VALVULAR LESIONS

The monopoly previously enjoyed by congenital defects for the facilities of open-heart surgery is being rapidly challenged by an increasing number of acquired lesions that are now amenable to successful repair. These are primarily acquired valvular deformities resulting from rheumatic fever. Even with the measures of prophylaxis against rheumatic fever that now are being implemented, significant reduction in the number of patients with rheumatic valvular disease cannot be expected for another 20 to 25 years, so that this area of responsibility for the cardiac surgeon remains vast.

McGoon, D. C.: "Open-Heart Surgery: Its Accomplishments and Challenges," *J. Med. Assn. Alabama*, 30:5, 1960.

Chemotherapy of Pulmonary Tuberculosis: The Management of Treatment Failures

REPORT OF THE COMMITTEE ON CHEMOTHERAPY AND ANTIBIOTICS
AMERICAN COLLEGE OF CHEST PHYSICIANS

Introduction

The selection of an appropriate drug regimen for the treatment of patients undergoing their initial course of chemotherapy for active pulmonary tuberculosis has become fairly well established. Isoniazid (INH) in adequate dosage, usually combined with one or more of the other first-line antituberculosis drugs, e.g., streptomycin (SM), para-aminosalicylic acid (PAS), is currently the drug treatment regimen of choice. However, the management of treatment failures is less well standardized and in many instances, continues to present a serious therapeutic enigma. The solution to this problem is of utmost importance not only for the individuals involved, but also to assure effective progress towards the ultimate eradication of foci of tuberculous infectiousness.

Accordingly, it was deemed advisable to prepare this report in an effort to consolidate current opinions concerning this subject in the light of the availability of newer drugs and of increasing experience with the use of the older ones. Suggestions relative to: (1) definition of treatment failures, (2) selection of drug regimens, (3) dosage and duration of treatment, will be presented. It is recognized that the application of any recommendation will be modified by factors of individual patient variation, e.g., drug hypersensitivity and liver or kidney damage.

1. *Definition:* "Treatment failures" are those drug-treated patients in whom a change of therapy is indicated because of failure to improve or in whom reactivation has occurred following a lapse of therapy. It may be due to one or more of a variety of intrinsic or extrinsic factors too numerous to be elaborated here. It is our opinion and recommendation that further treatment is best maintained in a hospital because of the contagiousness of the disease, to permit total re-evaluation of the patient's general condition, and to ensure close observation and adequate control.

2. *Selection of Antituberculosis Drugs:* Although many factors play important roles in the selection of an appropriate retreatment chemotherapeutic regimen, the more important considerations revolve around the adequacy or inadequacy of prior treatment, the underlying reason for changing ongoing therapy, known toxicity of, or hypersensitivity to drugs previously used, knowledge of the drug susceptibility status of the tubercle bacilli and the predicted need for thoracic surgical intervention. Recommendations for the selection of antituberculosis drugs in various circumstances of treatment failure are as follows:

a. If the duration of prior drug treatment be considered inadequate by current standards of treatment, the same drugs may be continued pending susceptibility reports.

b. If the treatment has been on a two-drug regimen and rapid progression of the disease is taking place, it is recommended that a first-line drug not previously used be added until susceptibility reports are obtained upon which to base future drug selection.

c. If the duration of prior drug treatment be considered adequate and triple-drug therapy (INH, SM/PAS) was used, it is recommended that the patient be treated with isoniazid plus a second-line drug, e.g., cycloserine (CS), pyrazinamide (PZA), or viomycin (VM), pending susceptibility information.

d. If the patient fails to respond to a course of triple-drug therapy currently being administered and tubercle bacilli are resistant to the three drugs used, it is recommended that a combination of CS, PZA, or VM be substituted. It is as yet too early to evaluate the possible role of kanamycin (KM) due to its high ototoxicity and renal toxicity. A newer antituberculosis agent, thioamide (THA), also is in need of further investigation.

e. Complete resistance to SM or to PAS implies lack of potential therapeutic efficacy and calls for discontinuation. However, complete resistance to INH does not have the same implication and this drug can be continued.

f. For those patients in whom it is deemed necessary to switch to a combination of second-line drugs, their short-term duration of effectiveness should be borne in mind and consideration given for thoracic surgical intervention at an early date, if feasible.

g. Oxytetracycline has been used as a replacement for PAS. The use of thiocarbanidin or streptovaricin cannot be recommended on the basis of reported clinical trials to date.

h. Further evidence through controlled studies is needed to verify the reported beneficial effects resulting from the addition of adrenocorticosteroids and corticotropin in the treatment of patients whose organisms are drug susceptible. It should be stressed that steroids should only be used in carefully selected cases with adequate chemotherapy employing known effective drugs.

3. *Dosage and Duration of Treatment:* Streptomycin is usually given 1 gm. daily or 1 gm. twice weekly. The dosage of isoniazid is 3 to 5 mg. per kg. of body weight/day. There is no incontrovertible evidence that higher dosages of INH are more effective than the standard INH dosage. If for any reason a higher dosage is employed, its use should be accompanied by a minimum of 50 mg. pyridoxine per day to reduce the risk of isoniazid neurotoxicity. In patients who are rapid inactivators of isoniazid, higher dosages of 21 to 24 mg./kg. have been reported to increase therapeutic efficacy. Sodium PAS is the generally preferred form of PAS (15 gm. of the salt, or 12 gm. of the acid daily).

In treatment failures, the use of CS in dosages higher than the conventional 0.25 gm. twice daily is clinically justified. The toxic effects of higher dosages on the central nervous system have been reported to be controlled, if not prevented, by concomitant administration of sedatives, anticonvulsants, and pyridoxine, singly or in combination.

The oral adult dosage of PZA is 20 to 40 mg./kg. per day. The conventional dosage for VM is 1 to 2 gm. twice weekly, intramuscularly. Oxytetracycline, as a replacement for PAS, is usually given in an oral dose of 1 gm. three times daily. KM at a dosage of 0.5 gm. twice daily i.m. may lead to deafness in a short period of time which limits its therapeutic value in any long-term program of treatment for tuberculosis. Reduction of this dosage, not to exceed 4.0 gm. weekly, has been reported to delay or prevent toxicity to the 8th nerve. The oral dosage of thioamide is 0.5-1.0 gm. daily, in divided doses.

The optimum duration of treatment is unknown. It should be emphasized that the second-line drugs are of short-term effectiveness of approximately 3 to 6 months' duration. Any plan of treatment with these drugs should include a program for thoracic surgical intervention at the earliest appropriate time. After inactivation has been reached, the duration of treatment should be longer than in original treatment patients.

COMMITTEE ON CHEMOTHERAPY AND ANTIBIOTICS
AMERICAN COLLEGE OF CHEST PHYSICIANS

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H. Corwin Hinshaw, San Francisco, California—*Vice Chairman*
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COLLEGE TO HOLD JOINT MEETING WITH AMA IN 1961
SCIENTIFIC SESSIONS TO EXTEND THROUGH MONDAY, JUNE 26

NOTE CHANGE IN DATES OF SCIENTIFIC SESSIONS

The 27th Annual Meeting of the American College of Chest Physicians will be held in New York City, Thursday, June 22 through Monday, June 26. Scientific sessions for the American College of Chest Physicians' 27th Annual Meeting will open on Saturday, June 24, 1961 instead of on Friday as in the past. A joint session with the Section on Disease of the Chest of the American Medical Association will be held on Monday, June 26. This will be the first joint meeting in the history of the two societies.

Headquarters for the College meeting will be the Commodore Hotel, New York City. The joint sessions with the AMA will be held at the Coliseum.

Now is the time to make your plans to attend this meeting.

COLLEGE INTERIM SESSION

The interim meeting of the College held at the Shoreham Hotel, Washington, D. C. on November 26-28 was very well received with 428 physicians and guests attending. The scientific program organized by Dr. Joseph W. Peabody Jr. and his committee was extremely interesting and the arrangements for the meeting were capably handled by Dr. Roy G. Klepser and the members of his committee. The Executive Council, Board of Regents and Board of Governors held their semi-annual meetings and a number of the College councils and committees arranged for special meetings during the session in Washington. The Clinical Meeting of the American Medical Association was held in Washington, November 28-December 1.

The Board of Regents of the College adopted the following resolution at its semi-annual meeting:

Whereas, Members of the American College of Chest Physicians in Cuba are having a difficult time, and

Whereas, It is becoming impossible for some of the most prominent physicians in that country to conduct their practices under the present regime, and

Whereas, The first chapter of the College to be organized outside of the United States was established in Cuba in the year 1940, and

Whereas, Many of the physicians have been loyal members of the College for more than twenty years, and

Whereas, The relations between our members in Cuba and those in the United States have always been on a most cordial and friendly basis, and

Whereas, Many of these physicians have left their country and are presently in the United States without funds, and

Whereas, It is urgent that assistance be rendered to these members of the College in the manner of loans to tide them over until such time as they can find employment,

Therefore be it Resolved, That the American College of Chest Physicians establish a special fund in the amount of $5,000.00 to be known as the "Cuban Relief Fund" and that members of the College, as well as other interested parties, be urged to contribute to this fund,

Be it Further Resolved, That this fund be used to assist worthy members of the College and their families who are presently exiled from Cuba.

The Board of Regents also adopted a resolution to support a scientific exhibit on "Physiologic and Clinical Testing of Cardiac Function" to be presented in the Section on Diseases of the Chest of the scientific exhibits of the American Medical Association in New York City, June 26-30, 1961. The exhibit is being produced by Dr. Rudolph E. Fremont, Chief, Cardiovascular Section, Veterans Hospital, Brooklyn, New York, with the help of the Medical Illustration Department and the Engineering Section of the Brooklyn VA Hospital, and is sponsored by the Committee on Cardiovascular Physiology, Council on Cardiovascular Research of the American College of Chest Physicians. Dr. John S. LaDue and Dr. Arthur M. Master are chairmen of the above-mentioned committee and council, respectively, which have officially endorsed the exhibit.

Reports of the following committees of the College were reviewed and acted upon by the Board of Regents at its semi-annual meeting:

Clinical Cardiovascular Disease
Cardiology in Children
Cardiovascular Physiology
Cardiovascular Surgery
Allergy
Bronchoesophagology
Chemotherapy and Antibiotics
Non-Surgical and Drug Therapy
Pulmonary Disease in Children
Pulmonary Surgery
Rehabilitation in Pulmonary Diseases
Occupational Disease of the Chest
Council and Committee on Undergraduate Medical Education

On Monday, November 28, the Board of Governors and Board of Regents held their semi-annual luncheon meeting. The following agenda of reports was presented at the meeting, presided over by Dr. Howell Randolph, Chairman of the Board of Governors:

Report on the Resident Loan Fund, M. Jay Flipse, Miami, Florida

Report of the Committee on Scientific Program
John F. Briggs, St. Paul, Minnesota and Howard S. Van Ordstrand, Cleveland, Ohio

Report on College Books, Burgess L. Gordon, Chicago, Illinois

Report of the Council on Postgraduate Medical Education
J. Winthrop Peabody, Sr., Washington, D. C.

Reports on International Activities of the College

Sixth International Congress on Diseases of the Chest, Vienna
Major General Oliver K. Niess, MC, USAF, Washington, D. C.

Post-Congress Conferences, Istanbul, Turkey and Tel Aviv, Israel
John F. Briggs, St. Paul, Minnesota

Post-Congress Conference, Athens, Greece
Peter A. Theodos, Philadelphia, Pennsylvania

Post-Congress Visit to Moscow and Leningrad, USSR
Henry C. Sweany, Mt. Vernon, Missouri

Council on International Affairs
Andrew L. Banyai, Chicago, Illinois, Chairman

Future International Congresses of the College
Murray Kornfeld, Chicago, Illinois

It was announced that the Seventh International Congress on Diseases of the Chest sponsored by the Council on International Affairs of the College would be held in New Delhi, India, February 20-24, 1963 and that the Eighth International Congress would be held in Mexico City in 1964.

Dr. Flipse, in his report on the Resident Loan Fund of the College, announced that funds were available for worthy young residents who need assistance during their resident training in diseases of the chest. He urged the Governors and Regents of the College to submit the names of any doctors they wish to approve for such loans. Applications for a resident loan may be obtained by writing to the Executive Offices of the College in Chicago.

CHAPTER NEWS

NEW CHAPTER OFFICERS

Georgia Chapter

President	Lawrence Lee, Jr., Savannah
Vice President	Walter G. Elliott, Cuthbert
Secretary-Treasurer	Robert H. Vaughan, Columbia

Indiana Chapter

President	Arvine G. Popplewell, Indianapolis
Vice President	Francis W. Hare, Madison
Secretary-Treasurer	John V. Thompson, Indianapolis

Japan Chapter

President	Susumu Hibino, Nagoya
Vice President	Shigeru Sakakibara, Tokyo
Secretary-Treasurer	Yuichiro Goto, Tokyo

Kentucky Chaper

President	Daniel N. Pickar, Louisville
Vice President	William H. Anderson, Harlan
Secretary-Treasurer	Daniel E. Mahaffey, Louisville

Korea Chapter

President	Chan Se Lee, Pusan
1st Vice President	Pill Whoon Hong, Seoul
2nd Vice President	Kyung Sik Kim, Seoul
Secretary-Treasurer	Pyoung Ki Kim, Seoul (re-elected)

New England States Chapter

President	Francis M. Woods, Boston (re-elected)
1st Vice President	Peter F. Harrington, Providence, R. I. (re-elected)
2nd Vice President	Emil Rothstein, Newton, Massachusetts
Secretary-Treasurer	Samuel Clive Cohen, Boston (re-elected)

New Jersey Chapter

President	A. A. Carabelli, Trenton
President-Elect	Emanuel Klosk, Newark
Vice President	Robert Henderson, Flemington
Secretary-Treasurer	Saul Lieb, Newark

Northern Chapter of South Africa

President	Denis N. Fuller, Johannesburg
Vice President	Bernard A. Horwitz, Johannesburg
Secretary-Treasurer	Gerhard K. Sluis-Cremer, Johannesburg

Pennsylvania Chapter

President	Archibald C. Cohen, Butler
Vice President	Robert L. Mayock, Philadelphia
Secretary-Treasurer	Howard E. Stine, Camp Hill

Middle East Chapter

Members and guests attending recent meeting of the Middle East Chapter in Bois-de-Boulogne, Lebanon.

President	Mardan Ali, Baghdad, Iraq
Vice President	Nicolas P. Naasan, Beirut, Lebanon
Secretary-Treasurer	Toufic Al-Awar, Beirut, Lebanon (re-elected)

Southern Chapter

President	DeWitt C. Daughtry, Miami, Florida
1st Vice President	Henry R. Hoskins, San Antonio, Texas
2nd Vice President	Joseph W. Peabody, Jr., Washington, D. C.
Secretary-Treasurer	William S. Klein, St. Louis, Missouri

Virginia Chapter

President	Charles G. Pearson, Charlottesville (re-elected)
Vice President	George E. Ewart, Richmond (re-elected)
Secretary-Treasurer	Cecil G. Smith, Catawba (re-elected)

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The joint program, developed by the Committee on Scientific Program of the American College of Chest Physicians and the Section on Chest Diseases of the American Medical Association, has been planned as an action of the Board of Trustees of the American Medical Association and the Board of Regents of the American College of Chest Physicians.

It is hoped the new arrangements will enable more members of the American College of Chest Physicians to stay over for the scientific sessions of the Section on Chest Diseases and visit the splendid scientific exhibits of the American Medical Association, which, for the first time, will open on Sunday afternoon, June 25.

The popular Fireside Conferences, also to be a joint session sponsored by both the American Medical Association and the College, will be held on Monday evening during the AMA meeting instead of on Friday evening as in the past. The equally popular round table luncheon meetings will also extend to Monday, June 26.

Headquarters for the College meeting will be the Commodore Hotel, New York City. The joint sessions with the AMA will be held at the Coliseum.

Now is the time to make your plans to attend this meeting.

MEDICAL SERVICE BUREAU

POSITION WANTED

Surgeon—thoracic surgeon, 35, American, AOA, progressive university residency, Board diplomate, F.C.C.P., F.A.C.S., dissatisfied with three years' solo private practice. Desires clinical-surgical association with group, clinic or medical school with teaching and some clinical research. Prefers southeast. Please address inquiries to Box 312B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Position available for medical director, 100-bed county tuberculosis sanatorium. Maintenance included, salary open. Apply to: George Schneider, President, Madison County Sanatorium, Edwardsville, Illinois.

Pulmonary Disease Service—two staff physician positions available on a 225-bed chest service with active medical, surgical and pulmonary functions. Salary from $10,635 to $17,000 p.a., depending on qualifications and experience. Living quarters available on station at moderate cost. Liberal retirement, vacation and sick benefits. Requirements: American citizenship, graduate of class A medical school, and a state board license. Address inquiries to the Manager, VA Center, Martinsburg, West Virginia.

Residents in pulmonary diseases wanted for July 1, 1961, in 600-bed hospital in the Ozarks. Fully certified, excellent facilities, research and teaching program, generous salary. Applicant must be in possession of ECFMG or provisional certificate. Write: Charles A. Brasher, M.D., Superintendent and Medical Director, Missouri State Sanatorium, Mt. Vernon, Missouri.

Staff physician wanted for pulmonary disease service, $782-950 month. San Francisco Bay Area hospital. Write: Alameda County Civil Service Commission, 12th and Jackson Streets, Oakland, California.

CALENDAR OF EVENTS

National and International Meetings

27th Annual Meeting, American College of Chest Physicians
Hotel Commodore, New York City, June 22-26, 1961

Seventh International Congress on Diseases of the Chest
New Delhi, India, February 20-24, 1963

Postgraduate Course

Postgraduate Course on Diseases of the Chest
Newark, New Jersey, March 1, 8, 15, 22, 1961

Chapter Meetings

New Jersey Chapter, Jersey City, February 28, 1961
Louisiana Chapter, New Orleans, March 10, 1961
New York State Chapter, New York City, March 24, 1961
Alabama Chapter, Tuscaloosa, April 12, 1961
Ohio Chapter, Cincinnati, April 12, 1961
Texas Chapter, Galveston, April 23, 1961
Arizona Chapter, Scottsdale, April 27, 1961

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For detailed information address

HENRY W. MALY, M.D., Director

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